Ligand-Controlled Selectivity in Palladium(0)-Catalyzed $C(sp^2)$-$C(sp^3)$ Negishi Cross-Coupling Reactions

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Prof. Dr. Olivier Baudoin
Prof. Dr. Frédéric Leroux

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Abstract

Over the past decades, transition-metal-catalyzed cross-coupling reactions have witnessed considerable growth and emerged as a powerful tool for the construction of carbon-carbon bonds. These reactions have found numerous applications in assembling structurally complex molecules ranging from medicines to materials. While the $C(sp^2)$-$C(sp^2)$ cross-coupling reactions have seen a tremendous development, less effort has been devoted to the more challenging $C(sp^2)$-$C(sp^3)$ couplings.

The selectivity control in the palladium(0)-catalyzed cross-coupling of alkyl nucleophiles is an important topic of research in the Baudoin group. Both direct and migrative cross-couplings can be achieved by simply switching the ligand involved.

Following the long-standing interest in this field, we firstly extended the migrative cross-coupling reactions to simple and easily available secondary alkyl bromides under Barbier conditions. Moreover, the terminal-selective functionalization of simple alkanes could be achieved when this reaction was coupled to a non-selective radical monobromination process.

On the other hand, a series of azole-based bulky phosphine ligands was designed and applied to direct $C(sp^2)$-$C(sp^3)$ Barbier-Negishi cross-coupling reactions, successfully preventing the β-hydride elimination process while favouring the direct reductive elimination.

Finally, the ‘‘ligand-controlled selectivity’’ strategy was applied to the divergent synthesis of enantioenriched β-amino acid derivatives.

Keywords: Negishi cross-couplings, palladium, $C(sp^2)$-$C(sp^3)$ bond formation, ligand-controlled, secondary alkyl bromides, Barbier conditions, enantiodivergence, β-amino acids

Ke-Feng Zhang
Prof. Dr. Olivier Baudoin group
Department of Chemistry
University of Basel
St. Johanns-Ring 19
CH-4056 Basel, Switzerland

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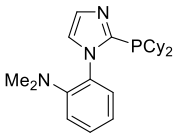
Abbreviations

Ac	Acetyl
Ad	Admantyl
Alk.	Alkyl
Aq.	Aqueous
Ar	Aryl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
Bu	Butyl
Cat.	Catalytic
Conc.	Concentrated
CPhos	2-Dicyclohexylphosphino-2′,6′-bis(*N,N*-dimethylamino)biphenyl
Cy	Cyclohexyl
Cyp	Cyclopentyl
dba	Dibenzylidene acetone
DCM	Dichloromethane
DFT	Density functional theory
DMAP	4-Dimethylaminopyridine
DMF	Dimethyl formamide
DMSO	Dimethyl sulfoxide
d.r.	Diastereoisomeric ratio
ee	Enantiomeric excess
e.g.	Exempli gratia
Et	Ethyl
e.r.	Enantiomeric ratio
e.q.	equivalent
ESI	Electron spray ionization
FG	Functional group
GC-MS	Gas chromatography mass spectrometry
h	hours
HPLC	High pressure liquid chromatography
HR-MS	High resolution mass spectrometry

i-Pr	*iso*-propyl
t-Bu	*tert*-butyl
IR	Infrared spectroscopy
L	Ligand
Me	Methyl
MeCN	Acetonitrile
NBS	*N*-bromosuccinimide
n-BuLi	*n*-butyllithium
s-BuLi	*sec*-butyllithium
t-BuLi	*tert*-butyllithium
NMR	Nuclear magnetic resonance
Ph	Phenyl
PEPPSI	Pyridine-enhanced precatalyst preparation, stabilization, and initiation
RT	Room temperature
sat.	Saturated
SM	Starting material
Nf	Nonaflyl
NHCs	*N*-heterocyclic carbenes
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	*N*,*N*-tetramethylethylenediamine
Piv	Pivaloyl
Pr	Propyl
Py	Pyridine
TBDPS	*tert*-Butyldiphenylsilyl
Tf	Triflyl
Pd^0/L	Palladium (0) bearing a ligand
rac	Racemate
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
UV	Ultraviolet
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

Catalogue of in-house ligands



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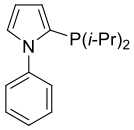

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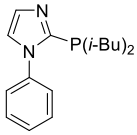

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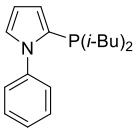

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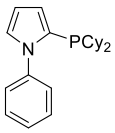

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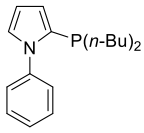

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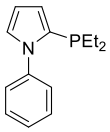

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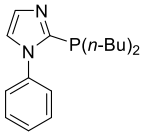

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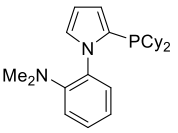

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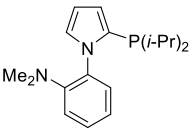

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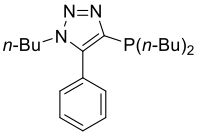

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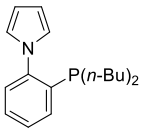

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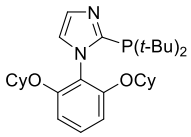

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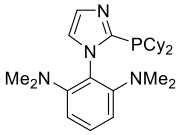

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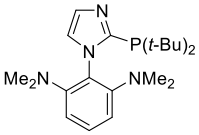

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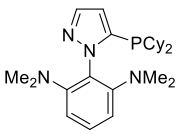

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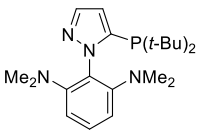

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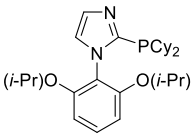

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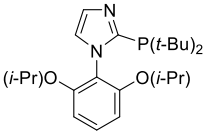

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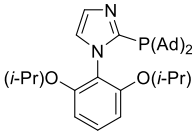

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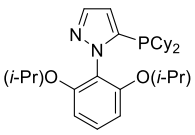

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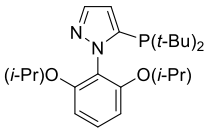

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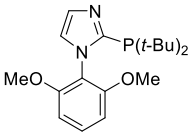

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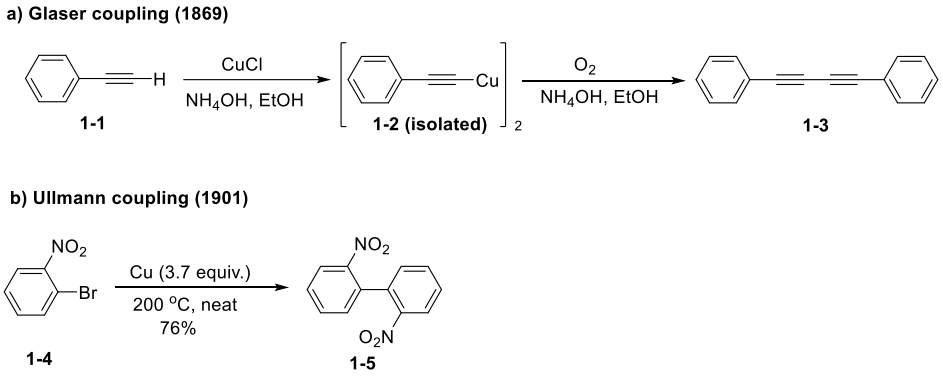
Chapter 1

Bibliographic part

1. Overview of metal-catalyzed cross-coupling reactions

1.1 Discoveries and developments

A coupling reaction is a general term for a variety of reactions where two hydrocarbon fragments are coupled with the aid of a metal catalyst. Historically, the first reported metal-catalyzed coupling reaction could date back to the 19th century, when Glaser discovered the homocoupling of aromatic acetylides in the presence of stoichiometric amounts of copper salts (Scheme 1.1a).[1] Following the development of C(sp)-C(sp) homocoupling, this method was extended to C(sp^2)-C(sp^2) bond formation. In 1901, Ullmann described the dimerization of 2-bromonitrobenzene promoted by excess copper (Scheme 1.1b).[2] Although harsh conditions were usually required for the early copper-mediated reactions, these discoveries paved the way for later developments.



Scheme 1.1. Glaser and Ullmann couplings

Over the past decades, metal-catalyzed cross-couplings, especially palladium-mediated transformations, have been developed rapidly and advances in recent years have greatly increased their scope and practicality. These findings revolutionized the way chemists construct molecules and provided new methods for previously impossible, but highly desirable carbon-carbon and carbon-heteroatom bond forming processes. Due to their great contribution to palladium-catalyzed cross-coupling reactions, Richard Heck, Ei-ichi Negishi and Akira Suzuki shared the Nobel Prize in chemistry in 2010.[3]

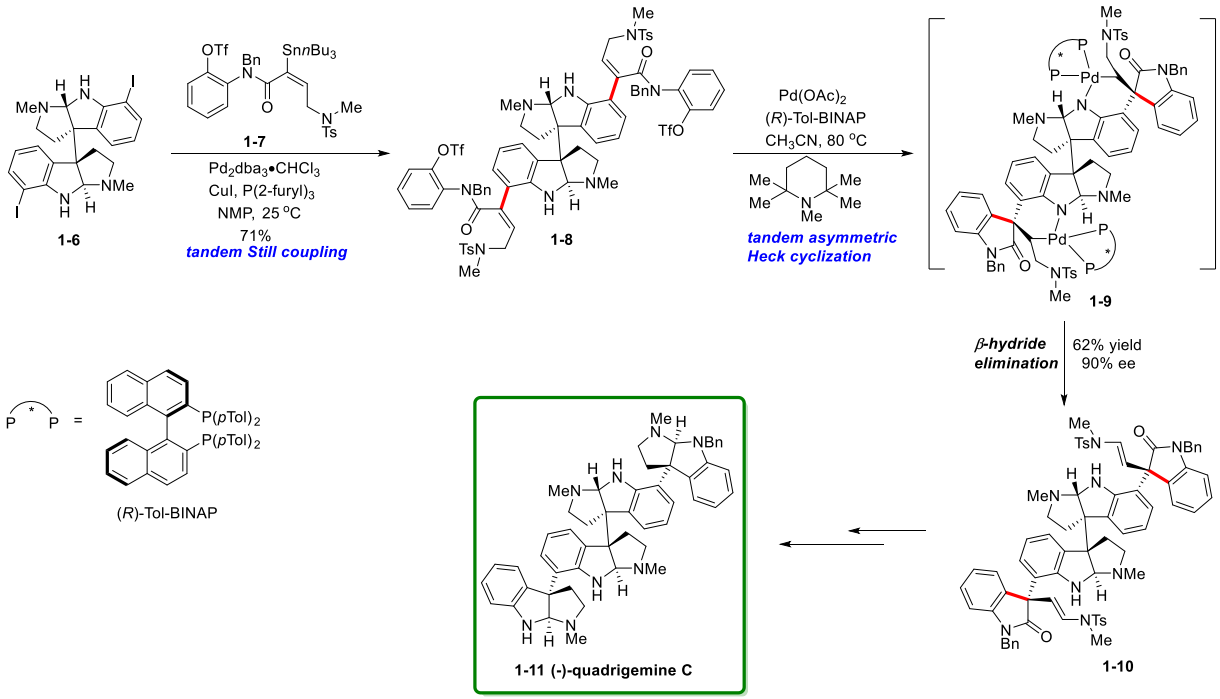
Since then, these discoveries inspired chemists to develop a broad range of additional cross-coupling reactions, such as C-H activation and decarboxylative couplings.[4] It is also noteworthy that a great deal of progress has been made on the development of asymmetric versions of cross-couplings.[5] In addition, "green" cross-coupling reactions are another

interesting research field. This includes the use of catalysts based on cheap and abundant transition metals,[6] as well as using water or ionic liquids as the reaction medium.[7] Given their essential role in carbon-carbon/heteroatom bond formation processes, cross-coupling reactions continue to attract attention from both the academic and industrial communities.

1.2 Applications in organic synthesis

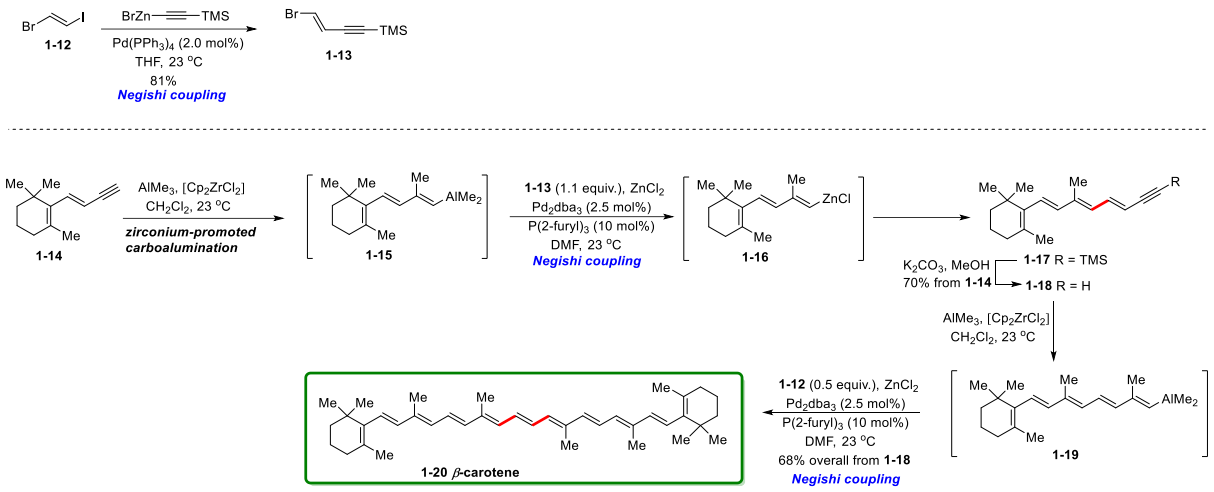
Due to their mild conditions associated with the reactions, together with their tolerance of a wide range of functional groups, cross-coupling reactions have had a great impact on synthetic organic chemistry and have found many applications in target-oriented synthesis. Among them, palladium-catalyzed cross-coupling reactions are the most prominent.[8]

Quadrigemine C is representative of the higher-order members of the pyrrolidinoindoline alkaloid family.[9] First described in 1987, quadrigemine C is reported to exhibit significant antibacterial and analgesic activities, and behave as a weak antagonist of the SRIF (somatostatin) receptor.[10] Therefore, the total synthesis of such a molecule is highly interesting and desirable. In 2002, the Overman group described an elegant synthetic route to the enantioselective total synthesis of quadrigemine C **1-11**, in which sequential tandem Stille couplings and catalytic asymmetric intramolecular Heck cyclizations were employed as the key steps (Scheme 1.2).[11]



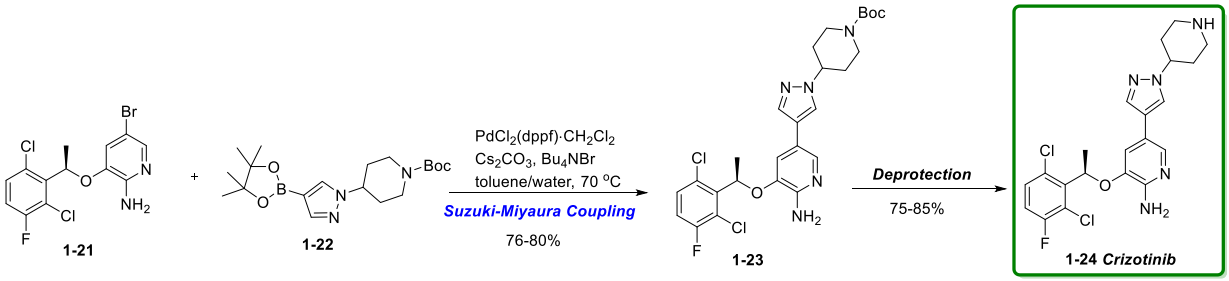
Scheme 1.2. Sequential tandem Stille couplings and asymmetric intramolecular Heck reactions in the enantioselective synthesis of (-)-quadrigemine C

An impressive example of application of Negishi couplings in total synthesis is the novel and general synthetic route to the β-carotenoids reported by the Negishi group. As shown in Scheme 1.3, these remarkable carbon-carbon bonds forming processes, each of which involved four different organometallic intermediates and three transmetallation steps (Zr→Al→Zn→Pd), proceed well with remarkable overall efficiency and stereoselectivity, affording the target molecule **1-20** in more than 99% stereoisomeric purity.[12]



Scheme 1.3. Application of Negishi coupling reaction in the total synthesis of β-carotene

In addition, the impact of palladium-catalyzed coupling reactions has been witnessed beyond academic field, particularly in the pharmaceutical industry.[13] One example is the synthesis of Crizotinib, a potent and selective Mesenchymal epithelial transition factor/Anaplastic lymphoma kinase (c-Met/ALK) inhibitor that is currently in phase III clinical trials. In 2011, Koning and co-workers from Pfizer reported a robust six-step process for the synthesis of Crizotinib, in which the highly selective Suzuki-Miyaura coupling could be conducted on a 50 kg scale (Scheme 1.4).[14]



Scheme 1.4. Application of the Suzuki-Miyaura coupling in industrial process

2. Palladium-catalyzed Negishi cross-couplings

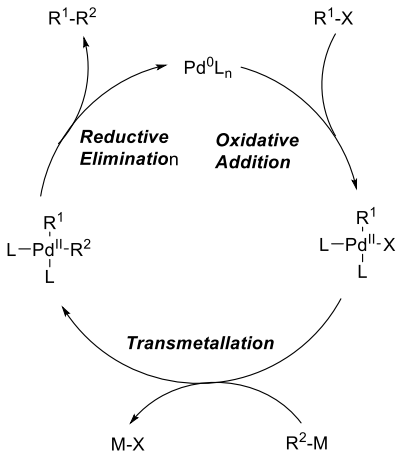
Negishi and co-workers originally studied the cross-coupling of organoaluminum reagents in 1976 employing palladium and nickel catalysts.[15] Later, they reported that organozinc compounds could be readily participated in Ni- or Pd-catalyzed cross-coupling reactions, providing a general and mild protocol for the preparation of unsymmetrical biaryls and diarylmethanes. It is noteworthy that the described reaction features high chemo- and regioselectivity as well as high cross-/homo-coupling ratios.[16] Although organozincs are air- and moisture-sensitive, a fact that has hindered their use compared to other cross-coupling reactions, their fast transmetallation to palladium compared to boronic acids allows the investigators to achieve Negishi cross-couplings between a wide range of unsaturated halides and organozincs under very mild conditions (Scheme 1.5). In addition, the low toxicity and easy preparation of organozinc compounds, as well as the increasing number of commercially available zinc reagents have greatly promoted the development and application of Negishi cross-coupling reactions in numerous fields.[17]

Palladium is the most often used transition-metal in Negishi cross-coupling reactions, but in some cases, palladium-based catalyst systems can also be replaced by alternative metals, such as Ni, Fe, Co, or Cu.[17] Considering the length of the bibliographic part and the focus of this thesis, mainly palladium catalysis will be discussed here.

Scheme 1.5. General scheme for Negishi couplings

2.1 Palladium-catalyzed Negishi cross-couplings of alkylzinc reagents

In general, transition-metal-catalyzed cross-coupling reactions undergo three consecutive steps as outlined in Scheme 1.6: oxidative addition, transmetallation and reductive elimination.



Scheme 1.6. General catalytic cycle for palladium-catalyzed cross-coupling reactions

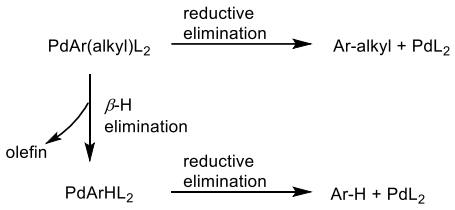
Due to the presence of an empty low-lying p orbital of zinc, the alkylzinc reagents exhibit an excellent ability to undergo transmetalation. Therefore, palladium-catalyzed Negishi cross-coupling reactions of alkylzincs have demonstrated to be powerful tools in numerous areas of synthesis.

However, the use of C(sp^3) organozincs in Negishi cross-coupling reactions has suffered from several serious problems. Consequently, although the Negishi protocol has been extensively studied using various coupling partners, such as alkynyl, aryl, alkenyl, allyl, and benzylzinc reagents, the frequent use of more challenging alkylzinc reagents containing β-hydrogen(s) as coupling partners has only attracted attention and been investigated more recently.[18]

2.2 Mechanistic studies on palladium-mediated Negishi cross-couplings

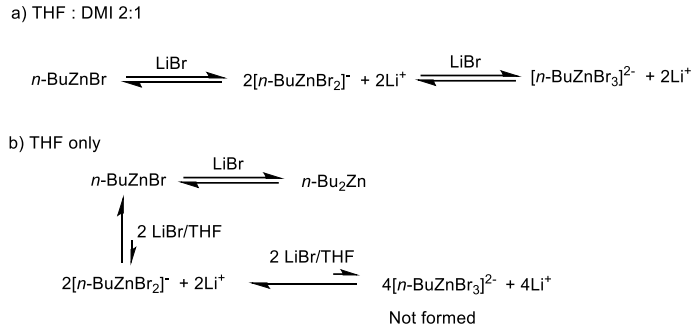
In light of the importance of Negishi cross-coupling reactions in synthetic organic chemistry, the study of their mechanism has been the subject of extensive investigation. In 2010, Knochel and Mayr groups studied the influence of the structures of both aryl halides and arylzinc reagents on the rate of various steps.[19] Competition experiments were conducted to determine these structure-reactivity relationships. The cross-couplings were found to be accelerated by electron acceptors on the aryl bromides and the accelerating effect decreases in the order *para* > *meta* > *ortho*. On the other hand, the presence of electron-acceptors on the arylzinc species diminished the reaction rate. Hammett correlations showed that substituents on the aryl bromides have a larger impact than the substituent variations on the arylzinc reagents (ρ = +2.5 VS. ρ = -0.98).

Espinet and co-workers reported a detailed study on the Negishi cross-coupling reaction of ArI (Ar = 2-$CO_2EtC_6H_4$) and Et_2Zn in the presence of two different palladium catalysts: conventional phosphine ligands (e.g. PPh_3) and hydride phosphine-electron-withdrawing olefin (P-EWO) ligands.[20] Their research provided useful insights into the two competitive pathways: reductive elimination giving rise to the cross-coupling product versus *β*-H elimination leading to the reduction product after subsequent reductive elimination (Scheme 1.7). With P-EWO ligands, the *β*-H elimination from the palladium complex is slow compared to the fast reductive elimination, thus favouring the formation of the cross-coupling product. However, in the presence of traditional phosphine ligands, the formation of reduction product is always a big problem.

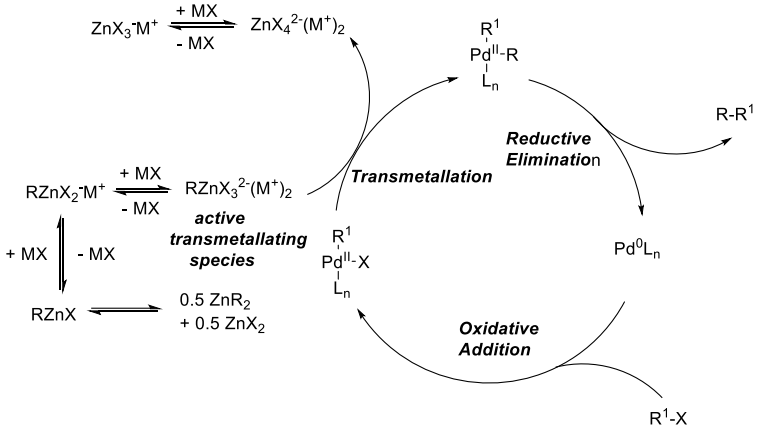


Scheme 1.7. Cross-coupling VS. reduction

Additionally, halide salts were reported to have a remarkable effect on Negishi cross-coupling reactions. In this regard, Organ and co-workers studied the charged zinc species that are formed upon addition of LiBr to *n*-BuZnBr in different solvents.[21] They disclosed that less polar solvents, like THF, do not allow the formation of *n*-$BuZnBr_3^{2-}$ and the Schlenk equilibrium shifts toward *n*-Bu_2Zn, which is not the active transmetallation species in Negishi cross-couplings (Scheme 1.8b**)**. On the contrary, in a mixed solvent system (THF/DMI 2/1), the Schlenk equilibrium tends to form a highly charged organozinc species *n*-$BuZnBr_3^{2-}$ (Scheme 1.8a). Based on these studies, they proposed the following catalytic cycle as described in Scheme 1.9 for the alkyl–alkyl Negishi reaction. On the other hand, the Clyburne group developed a method to prepare and identify $RZnX_3^{2-}$ species, which allowed the cross-coupling to occur in the absence of added metal salts and polar co-solvent.[22]



Scheme 1.8. Schlenk equilibrium involved in Negishi cross-couplings



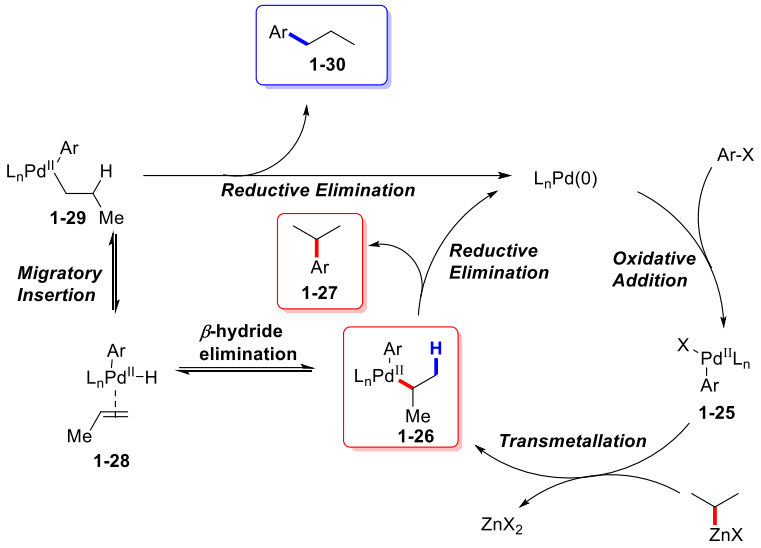
Scheme 1.9. Proposed catalytic cycle for the alkyl–alkyl Negishi reaction

However, a significantly different phenomenon was observed in the reaction system of arylzinc compounds.[23] Diarylzinc reagents were found to have the ability of transmetallation in low dielectric solvent (such as THF) without the aid of salt, whereas ArZnX compounds behaved differently, requiring either a high dielectric solvent or a lower polarity solvent aided with enough salt. Moreover, unlike the alkylzinc systems for which higher-order zincates are needed to facilitate the transmetallation step, there is no evidence of a similar requirement in the cross-coupling of arylzinc reagents.

3. Site-selectivity issues in palladium-catalyzed Negishi cross-couplings of secondary alkylzinc reagents

The palladium-catalyzed Negishi cross-couplings involving secondary alkylzincs remain challenging. A major limitation arises from the competitive β-hydride elimination and migratory reinsertion that resultes in the formation of undesired isomers.[18] A simplified mechanism for the reaction of an *iso*-propyl organozinc with an aryl halide is shown below (Scheme 1.10). The reaction is initiated by oxidative addition of a palladium(0) complex with

an aryl halide, which is then followed by transmetallation with a secondary alkylzinc, producing intermediate **1-26**. At this stage, direct reductive elimination would afford the branched product **1-27** and regenerate the palladium(0) complex for the next catalytic cycle. Alternatively, the competitive *β*-H elimination can occur reversibly to form intermediate **1-28**. It then undergoes a migratory insertion step to produce the linear palladium (II) complex **1-29**, which can then reductively eliminate to give the isomerized product *n*-PrAr **1-30**.



Scheme 1.10. Mechanism for the palladium(0)-catalyzed Negishi cross coupling of *iso*-propylzinc halide with an aryl halide

From the mechanism, it is clear that controlling the rate of direct reductive elimination relative to *β*-H elimination is an important factor to achieve a better site-selectivity. Previous studies have shown that the structure of ligands has a great effect on this competition. Over the last decades, various ligands and catalyst systems have been developed to supress the migration pathway and favour direct cross-couplings. In the meantime, the Baudoin group has a long-standing interest in migrative cross-couplings, which provide a new catalytic approach to functionalize unactivated C-H bonds at remote positions of alkyl chains.[24]

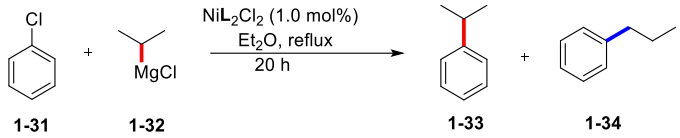
3.1 Direct cross-couplings

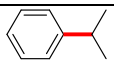
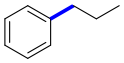
3.1.1 Development of phosphine ligands

To address the issue of *β*-H elimination during the reaction pathway, studies from several groups demonstrated that the *β*-H elimination and migratory pathway can be limited by employing catalysts containing bulky phosphine ligands that increase the steric bulk around palladium, which can then favour the reductive elimination.

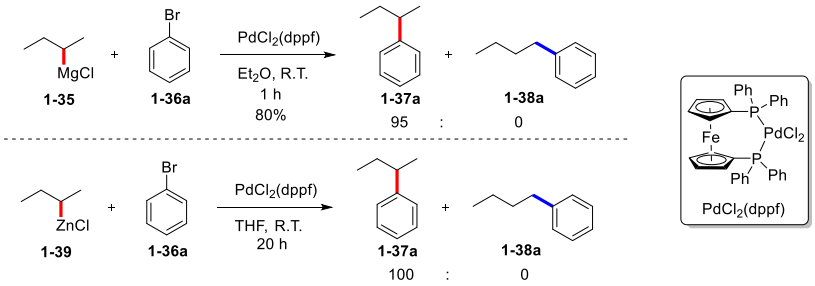
In 1972, Kumada/Tamao reported that nickel-diphosphine complexes could couple secondary alkyl Grignard reagents with a limited number of aryl halides.[25] They discovered that the extent of isomerization strongly depends on the electronic nature of the phosphine ligand in the catalyst (Table 1.1). While dppe and dppp gave the direct coupling product in good yield and excellent selectivity (entry 1& entry 2), changing of diphosphine ligand to dmpe afforded mainly the migrated linear product (entry 3).

Table 1.1. Ligand effect in nickel-catalyzed cross-coupling of secondary alkyl Grignard reagents with aryl halides



Entry	$\mathbf{L}_2$ in catalyst	Total yield	 1-33	 1-34	
1	$Ph_2PCH_2CH_2PPh_2$ (dppe)	74%	96	4	0
2	$Ph_2PCH_2CH_2CH_2PPh_2$ (dppp)	89%	96	4	0
3	$Me_2PCH_2CH_2PMe_2$ (dmpe)	84%	9	84	7

Later, in 1984, [1,1 '-bis(diphenylphosphino)ferrocene] palladium(II) [$PdCl_2$(dppf)] was found to be an active and selective catalyst for the cross-coupling of secondary and primary alkyl Grignard and alkylzinc reagents with organic halides (Scheme 1.11).[26]

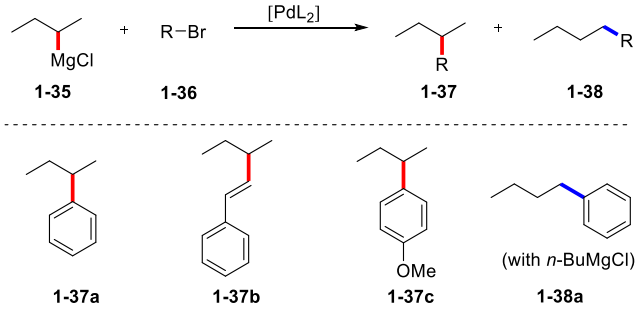


Scheme 1.11. Grignard and Negishi couplings of secondary alkyl organometallics catalyzed by $PdCl_2$(dppf)

Further studies showed that the selectivity and activity of the palladium complexes with bidentate phosphine ligands are strongly dependent upon the molecular framework lying

between the two diphenylphosphino groups in the ligand. As shown in Table 1.2, the values of the P-Pd-P and Cl-Pd-Cl angles in the complexes may well correlate with the activity and selectivity of the palladium complexes: the larger P-Pd-P and smaller Cl-Pd-Cl angles, the faster is the reductive elimination to form the direct cross-coupling product.

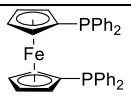
Table 1.2. P-Pd-P and Cl-Pd-Cl angles in $PdCl_2L_2$ complexes and their activities in the cross-coupling



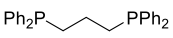
1-35 1-36 1-37 1-38

1-37a 1-37b 1-37c 1-38a

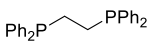
Entry	$PdCl_2L_2$	Angle, deg.		Yield, %			
		P-Pd-P	Cl-Pd-Cl	**1-37a**	**1-37b**	**1-37c**	**1-38a**
1	$PdCl_2$(dppf)	99.07	87.8	95	97	75	92
2	$PdCl_2$(dppp)	90.6	90.8	43	76	4	12
3	$PdCl_2$(dppe)	85.8	94.2	0-4	3	-	3



dppf

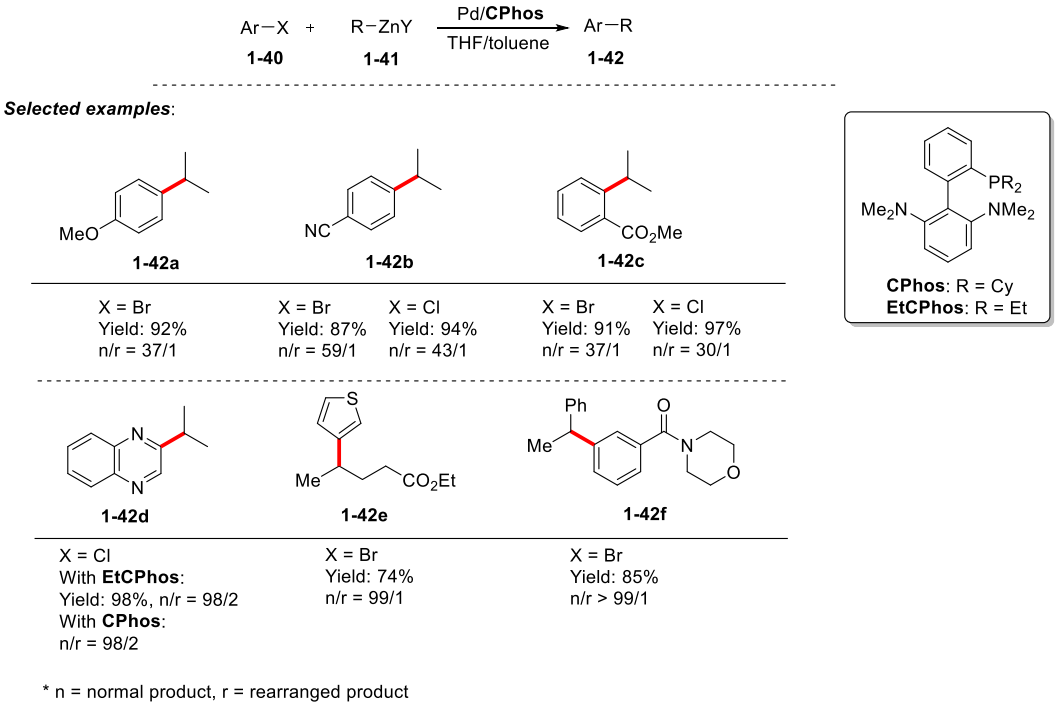


dppp



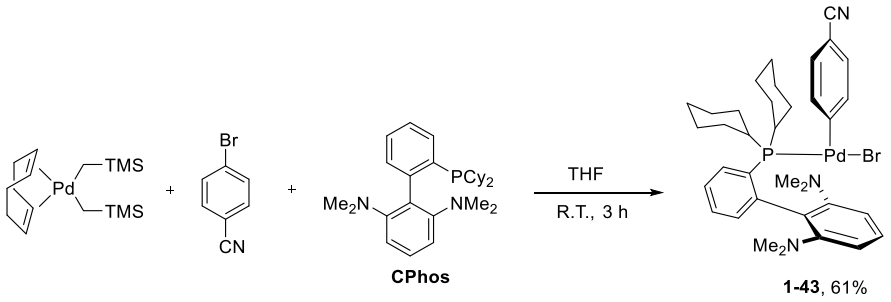
dppe

Because of the important role of ligands in controlling the selectivity, different types of phosphine ligands were developed and applied to the coupling of secondary alkyl organometallics, such as the bulky monodentate phosphine ligands tri-*tert*-butylphosphine P(*t*-Bu)$_3$[27] and cataCXium A *n*BuPAd$_2$[28]. In addition, an elegant work reported by the Buchwald group detailed the palladium-catalyzed Negishi coupling of secondary alkylzinc halides with aryl bromides, activated aryl chlorides and heteroaryl halides using bulky CPhos-type ligands. Under their optimal conditions, good to excellent ratios of direct to migrative (isomerized) coupling products were observed for a variety of substrates (Scheme 1.12).[29]



Scheme 1.12. C(sp^2)-C(sp^3) Negishi cross-couplings with CPhos-type ligands developed by the Buchwald group

To have a better understanding of the unique activity and selectivity of palladium-based catalyst system featuring CPhos-type ligands, an air-stable oxidative addition complex [**L**·ArPdBr] (Ar = 4-cyanophenyl) **1-43** was prepared and studied (Scheme 1.13). First of all, catalytic amount (1 mol%) of complex **1-43** was engaged in the reaction of methyl-4-chlorobenzoate and *iso*-propylzinc bromide, giving the same ratio of direct and migrative products as when a palladacycle precatalyst featuring CPhos was used. They believe that this demonstrated the catalytic competence of **1-43** for the coupling of secondary alkylzinc halides.



Scheme 1.13. Preparation of oxidative addition complex featuring CPhos

The X-ray structure of **1-43** (Figure 1.1) showed a nearly square-planar Pd(II) center featuring k^2 bound CPhos ligand through P atom and *ipso*-C moiety of the bottom aromatic ring

(*ipso*-C-Pd bond length = 2.478(3) Å). In addition, the solid-state structure of **1-43** indicates the monodentate nature of CPhos, since neither of the two dimethylamino substituents coordinates to the Pd(II) center. Further examination of complex **1-43** suggests that neither of the two dimethylamino groups lies in the plane of the bottom ring of CPhos. This probably discloses that the lone pair of the Me_2N- group is not conjugated with the lower ring of CPhos and the two Me_2N- group could probably act as electron-withdrawing substituents, thereby rendering the bottom ring of CPhos less electron-donating. Based on these results, they believed that the use of CPhos-type ligand in the coupling of secondary alkylzincs may facilitate the reductive elimination and that carefully balancing the electron-donating ability of P-bound substituents and the biaryl backbone is critical to obtain good selectivities.

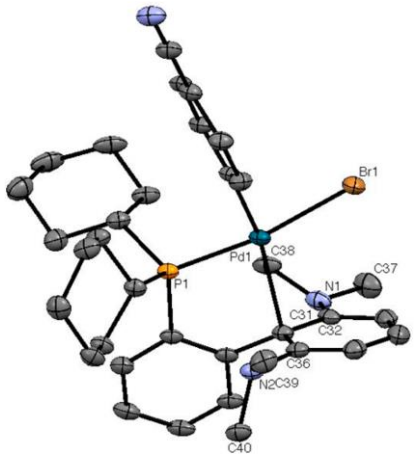


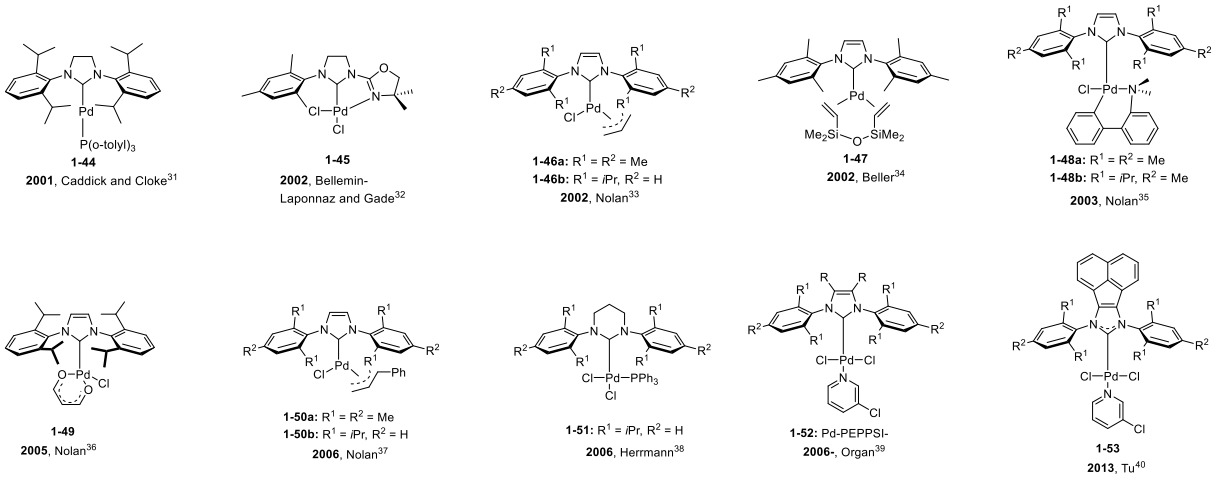
Figure 1.1. X-ray structure of **1-43**

3.1.2 Development of N-heterocyclic carbene ligands

Besides phosphine ligands, the search for different cross-coupling catalyst systems turned chemists' attention to the use of N-heterocyclic carbene (NHC) ligands.[30] NHC ligands have shown many different interesting characters compared to phosphine ligands. The thermal stability of Pd-NHC bonds is relatively high. In addition, NHC ligands usually provide a longer catalyst lifetime and a consistent reactivity throughout the course of the transformation, since the strong binding of the electron-rich carbene to the metal center helps the palladium retain its ligand.

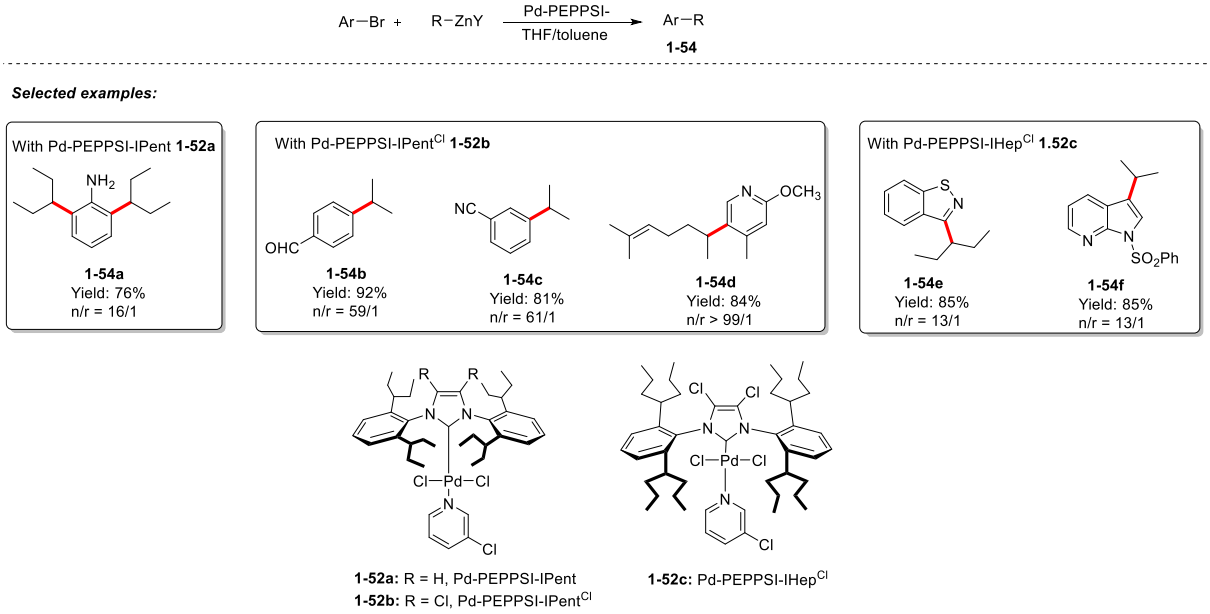
Therefore, numerous monoligated palladium NHC complexes have been designed and applied to cross-coupling reactions (Scheme 1.14). In general, the bulkier the NHC catalysts, the higher is the catalytic activity.[41] Of note, Pd-PEPPSI type complexes (PEPPSI is an acronym for pyridine-enhanced precatalyst preparation, stabilization, and initiation) developed by

Organ and co-workers showed comparable activity and selectivity and established them as successful alternatives to palladium phosphine complexes in cross-coupling reactions.[30a, 30d]



Scheme 1.14. Selection of monoligated palladium NHC-complexes used in palladium-catalyzed cross-couplings

Pd-PEPPSI-series complexes have found great applications in not only carbon-carbon bond formation, but also carbon-heteroatom bond formation. Particularly, some of these NHC ligands could suppress the β-hydride elimination process efficiently and afford the desired, direct coupling products in good to excellent selectivities (Scheme 1.15). DFT studies suggest that the relative energy barrier difference between reductive elimination and β-hydride elimination correlates very well with the observed selectivities. In addition, the effect imparted to the NHC substituents is primarily due to sterics.[41b, 42] Therefore, bulky Pd-NHC catalysts, like Pd-PEPPSI-IPent[39b], Pd-PEPPSI-IPent^{Cl} [39c] and Pd-PEPPSI-IHep^{Cl} [39d] were designed, showing great selectivity for the reactions of a wide range of secondary alkylzincs and highly functionalized aromatic and heteroaromatic halides.



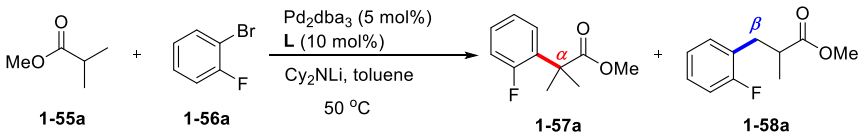
Scheme 1.15. Pd-PEPPSI catalyzed Negishi couplings of secondary alkylzincs

3.2 Migrative cross-couplings developed in the Baudoin group

3.2.1 Initial discovery and mechanistic understanding

In 2010, the Baudoin group studied the Pd-catalyzed arylation of isobutyric esters.[43] Initial attempts showed that ligands have a great effect on the selectivity for the α- or β-product (Table 1.3). Whereas the bulky phosphine ligands P(*t*-Bu)$_3$ gave rise to the direct coupling product (entry 1), more flexible ligands afforded a completely reversed selectivity, generating β-arylated product **1-58a** (entries 3-8).

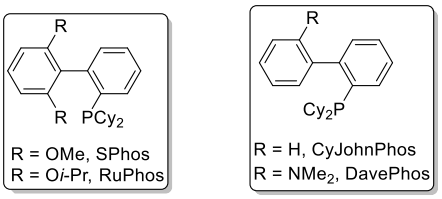
Table 1.3. Effect of the ligands on the Pd-catalyzed arylation of isobutyric esters



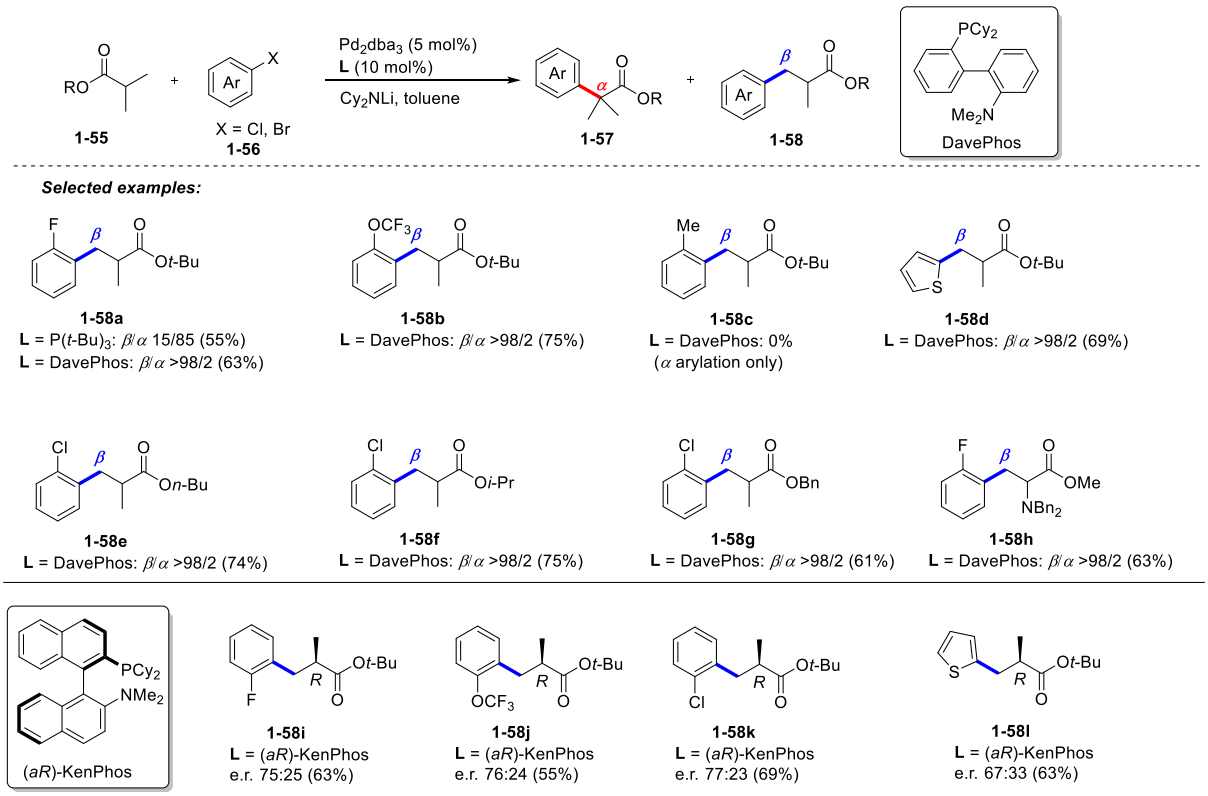
Entry	Ligand	Conversion (%)[a]	α/β[a]	Yield (%)[a]
1	P(t-Bu)$_3$·HBF$_4$	100	85/15	55%, α
2	PCy$_3$·HBF$_4$	6	n.d.	<1
3	PCy$_3$·HBF$_4$, 110 °C	100	<1/99	71%, β
4	SPhos	100	3/97	>95%, β
5	RuPhos	100	1/99	>95%, β

6	CyJohnPhos	100	1/99	>95%, β
7	DavePhos	100	<1/99	>95%, β
8	DavePhos, 28 °C	100	<1/99	>95%, β

[a] Determined by GC-MS.



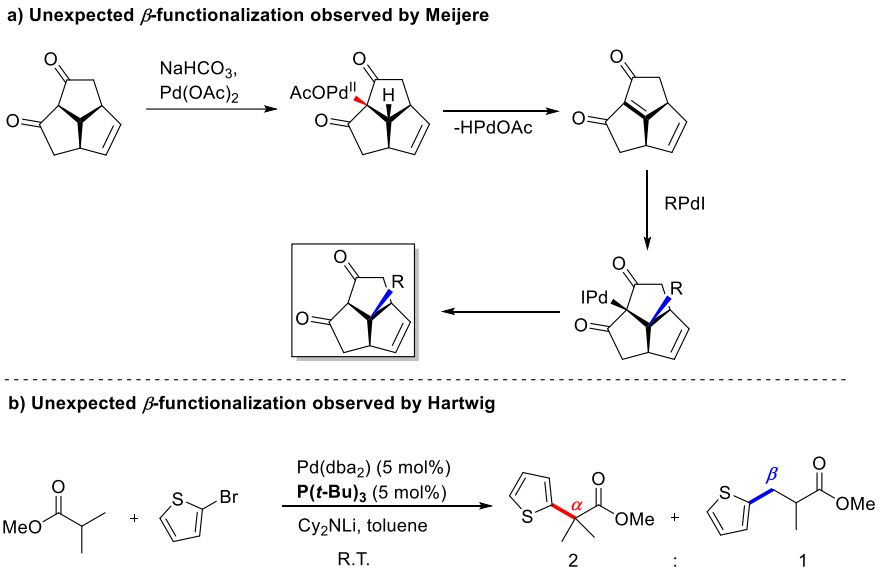
However, only aryl halides with *ortho*-electron withdrawing substituents (**1-58a**, **1-58b** VS. **1-58c**) or a heteroatom (O, S) at the adjacent position (**1-58d**) to the C-X bond gave a high selectivity for the β-products. A wide range of ester groups (**1-58e** to **1-58h**) were well tolerated under the optimal conditions. Finally, the asymmetric version of this transformation was also investigated, albeit with moderate enantioselectivities in most cases (**1-58i** to **1-58l**).



Scheme 1.16. Scope and limitations of Pd-catalyzed arylation of isobutyric esters

The unexpected β-arylation under the current catalytic conditions attracts our attention. To the best of our knowledge, only two examples of similar observations have been reported before. In 1996, Meijere group observed an unexpected palladium-catalyzed substitution on the

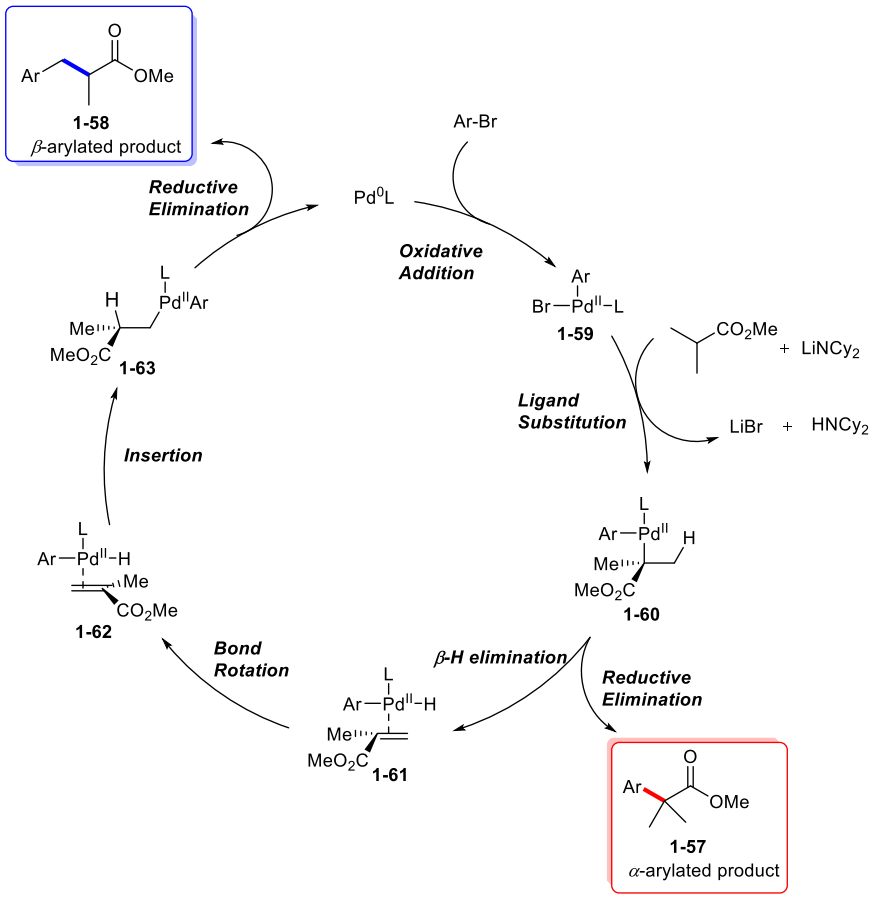
triquinanedione system (Scheme 1.17a).[44] Since the oxidation of ketones and diketones to *α*, *β*-unsaturated compounds by palladium acetate is a known reaction, they assumed that *α*, *β*-unsaturated 1,3-diketone was formed as an intermediate, which was then followed by palladium reinsertion, generating the *β*-functionalized product. Another example was reported by the Hartwig group in 2002 (Scheme 1.17b).[45] While studying the palladium-catalyzed arylation of *α*, *α*-disubstituted esters, a 2:1 mixture of *α*- and *β*-arylated products was obtained in the reaction of methyl isobutyrate with 2-bromothiophene. Since this phenomenon was only observed with bromothiophene, they proposed that the reductive elimination from electron-rich thiophenylpalladium enolate intermediate is slower compared to the analogous intermediates formed from aryl or other heteroaryl bromides. Due to the slower reductive elimination, the transformation of the hindered palladium enolate to a less hindered homoenolate occurred, which then afforded the *β*-arylated product after subsequent reductive elimination.



Scheme 1.17. Overview of previously reported unexpected *β*-functionalization

To gain further insight into the unexpected *β*-selectivity, our group conducted in-depth mechanistic studies in collaboration with the group of Prof. Eric Clot (University of Montpellier).[46] DFT calculations were performed in order to give insights into the selectivity resulting from the presence of different ligands. It was found computationally that with PCy_3, the reductive elimination leading to *α*-arylated product was disfavoured ($\Delta G^{\neq}$ = 23.5 kcal. mol^{-1} with 1-bromo-2-fluorobenzene) over the *β*-arylation pathway ($\Delta G^{\neq}$ = 19.8 kcal. mol^{-1}).

Based on these studies, the mechanism described in Scheme 1.18 was proposed. The mechanistic cycle starts with oxidative addition between aryl bromide and catalytic palladium (0) species, forming palladium (II) species **1-59**, which then undergoes ligand substitution to give intermediate **1-60**. At this point, two possible pathways could occur depending on the catalytic system and also on the substrate. Direct reductive elimination affords the classical α-arylated product **1-57**. In the meantime, with a suitable ligand, the palladium homoenolate intermediate **1-63** could be formed via a sequence of β-H elimination/bond rotation/reinsertion. Subsequent reductive elimination would result in the formation of β-product **1-58** and regeneration of the active palladium (0) species for the next catalytic cycle.

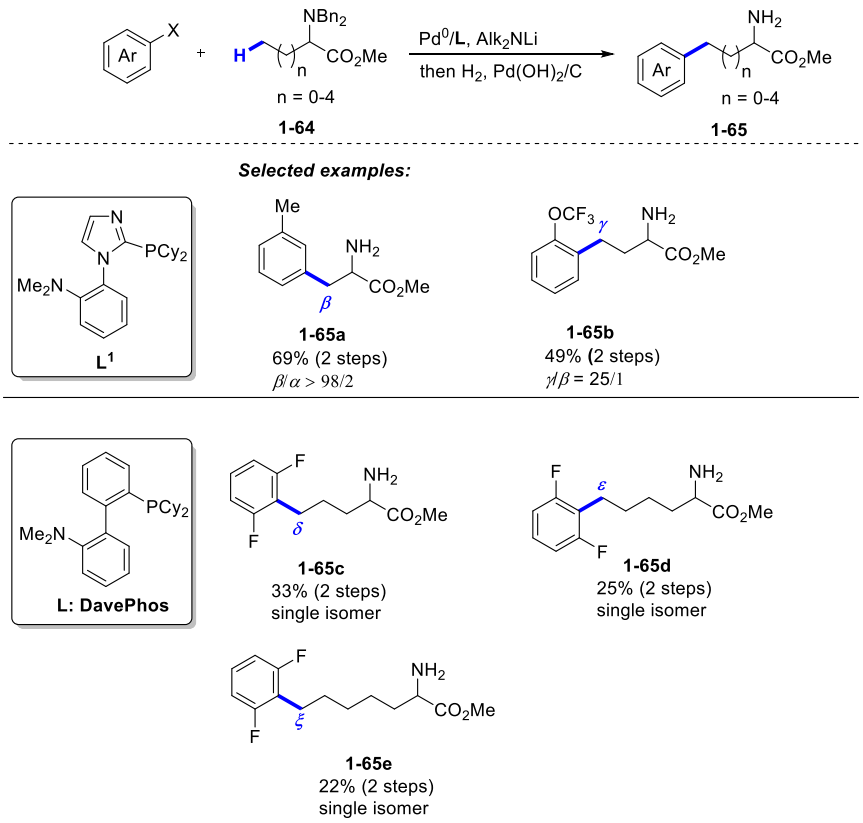


Scheme 1.18. Mechanistic cycle for β–arylation of methyl isobutyrate

3.2.2 Developments of migrative cross-couplings in other enolate systems

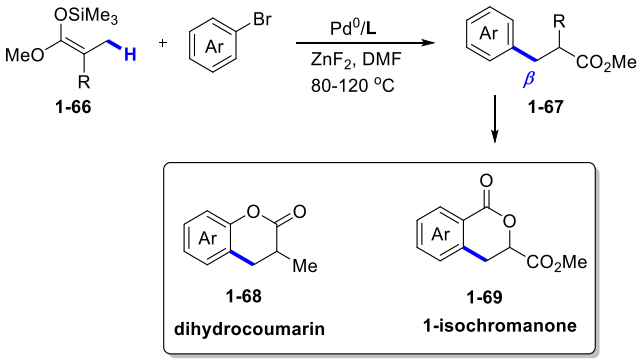
In addition to isobutyrates, this migrative cross-coupling strategy was also extended to the long range C-H arylation of α-amino esters, which occurred selectively at the terminal

position of the alkyl chain thanks to a fine-tuning of the ligand structure, giving rise to a broad scope of synthetically useful (hetero)arylalanines and homologues (Scheme 1.19). [47]



Scheme 1.19. Migrative arylation of α-amino esters

To further extend the scope of migrative cross-couplings, silyl ketene acetals (SKAs) were chosen as competent nucleophiles.[48] SKAs are believed to be stable and isolable surrogates of ester enolates and they are less reactive than the corresponding lithium enolates. The β-arylation of SKAs furnished a milder protocol, thus allowing the possibility of synthesizing more functionalized compounds with sensitive groups. The synthetic value of this methodology was further demonstrated by the easy transformation of the products into valuable benzofused δ-lactones such as 1-isochromanones and dihydrocoumarins (Scheme 1.20).

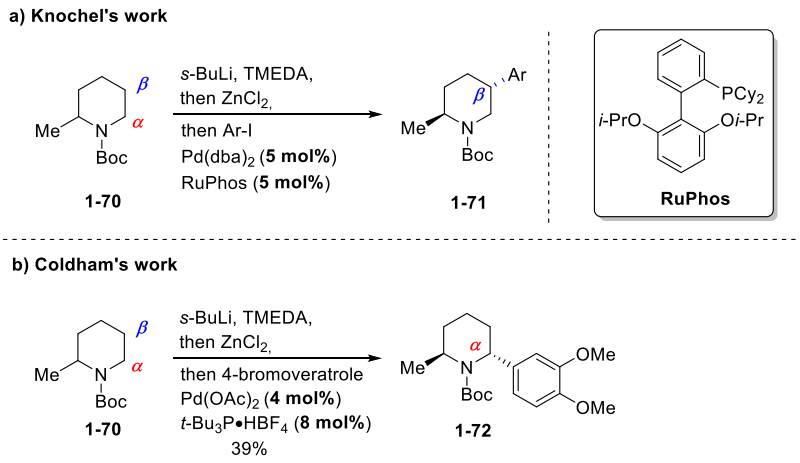


Scheme 1.20. Migrative cross-couplings of silyl ketene acetals

3.2.3 Developments of migrative cross-couplings in Negishi reactions

β-hydride elimination is still a challenging issue in palladium-catalyzed C(sp^2)-C(sp^3) Negishi cross-couplings. As stated before, previous studies were mainly focused on suppressing this process. On the other hand, taking advantage of *β*-hydride elimination step and the migratory pathway to realize remote functionalization is less developed.[24]

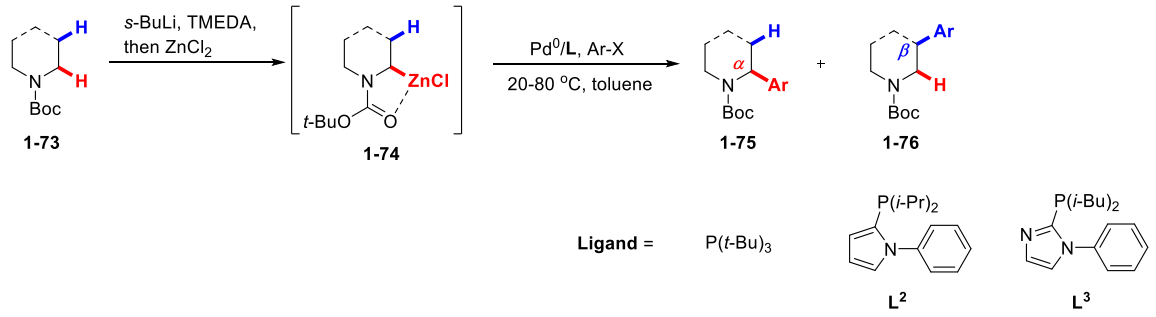
In 2010, while studying the diastereoselective arylation of substituted Boc-piperidines, Knochel and co-workers discovered that unexpected *β*-arylated products were obtained when 2-methyl piperidine was used (Scheme 1.21a).[49] They assumed that the reaction proceeds through *β*-hydride elimination and the Pd 1,2-migration/cross-coupling sequence seems to be affected by the nature and stoichiometry of the phosphine ligand, since no migration occurred in Coldham's catalyst system ($Pd(OAc)_2$/*t*-Bu_3P with a ratio of 1:2) (Scheme 1.21b).[50]



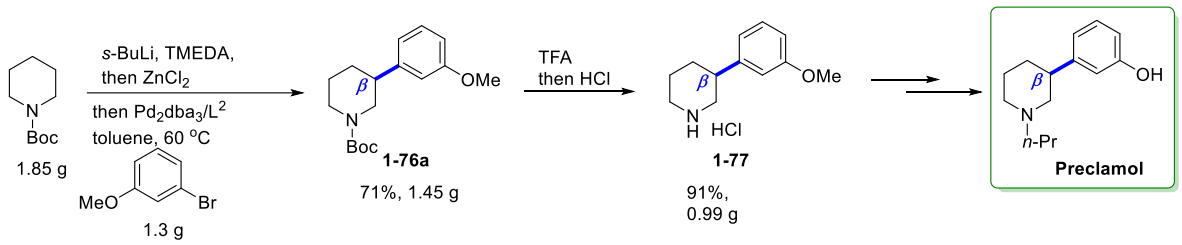
Scheme 1.21. Studies on arylation of *N*-Boc-piperidines by Knochel and Coldham groups

In line with previous efforts to develop migratory cross-couplings and the in-depth mechanistic analysis in this field, the Baudoin group developed an elegant work on

ligand-controlled selective arylation of α-zincated cyclic[51] and acyclic *N*-Boc-amines[52] (Scheme 1.22), giving rise to a variety of synthetically useful β-arylated amines, such as the drug candidate preclamol (Scheme 1.23). The selectivity for α- VS. β-arylation was controlled by the ligand, with bulky and rigid phosphine ligands providing normal α-arylated product, whereas more flexible *N*-phenylazole-based phosphine ligands induced majorly β-arylation.



Scheme 1.22. Direct & migrative Negishi couplings of cyclic and acyclic *N*-Boc-amines



Scheme 1.23. Formal synthesis of preclamol using migrative Negishi couplings

4. Research aim and challenges

Palladium-catalyzed C(sp^2)-C(sp^3) cross-couplings are particularly valuable tools in synthetic chemistry and hence a great deal of interest has emerged in this area. Although great progress has been made over the last decades, challenges still exist in this regard, e.g. preformation of organometallic species, site-selectivity due to β-H elimination. The aim of this Ph.D. thesis was to further study the selectivity control in the palladium(0)-catalyzed cross-couplings of secondary alkylzinc reagents and apply this strategy to prepare synthetically useful organic intermediates.

In the first part, we extended the migrative cross-couplings to simple and easily accessible secondary alkyl bromides, expecting to functionalize the C(sp^3)-H bond at the remote position.

In the second part, based on previous studies, a series of azole-based bulky and rigid phosphine ligands was designed and applied to direct C(sp^2)-C(sp^3) Negishi cross-couplings.

Finally, based on the "ligand-controlled selectivity" strategy, an enantioselective divergent arylation of *N*-Boc-1,3-oxazinanes was successfully developed. The application potential of this methodology has been further demonstrated in the divergent synthesis of enantioriched β^2- and β^3-amino acids.

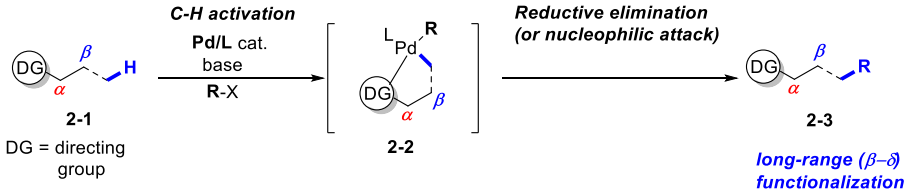
Chapter 2

Terminal-selective functionalization of alkyl chains by regioconvergent cross-coupling

1. Introduction and research plan

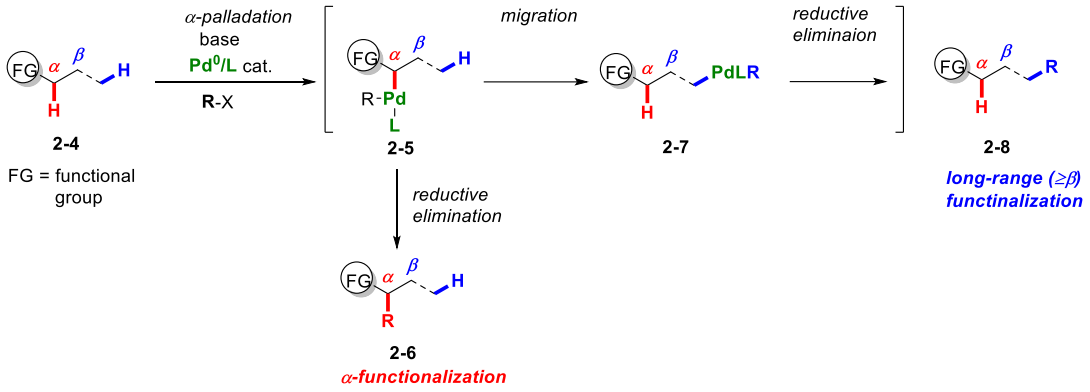
1.1 Remote functionalization strategies

The direct and selective functionalization of hydrocarbon chains at the remote positions provides a step-economic strategy to make functionalized molecules from easily accessed feedstocks.[4a] Consequently, tremendous efforts have been made towards the direct functionalization of C-H bonds to useful C-X (X = C, O, N, etc.) bonds. Site-selectivity is a particularly challenging issue within this research field. To solve this problem, different strategies have been developed over the past decades.[53] Among them, employing a directing group (Scheme 2.1) is greatly pursued,[54] and therefore, numerous monodentate and bidentate directing groups were designed and developed, and found many applications in organic synthesis. Despite the impressive number of contributions and the achievements obtained, there are still significant demand and great limitations in this area. One of the disadvantages is that this method is only limited to the formation of small palladacycles (usually four- to six-membered).



Scheme 2.1. Remote C-H functionalization by installing a directing group

On the other hand, the Baudoin group developed a new strategy of remote C-H functionalization based on the migration of an organopalladium species along an alkyl chain (Scheme 2.2**)**.[24] This type of reaction is initiated by α-palladation via the sequence of deprotonation at the acidic α C-H bond/oxidative addition with R-X, forming the intermediate **2-5**. At this stage, reductive elimination directly affords α-functionalized product **2-6**. Alternatively, Baudoin group discovered that a suitable ligand or substrate could force the branched intermediate **2-5** to form the terminal palladium complex **2-7** via a β-H elimination/rotation/insertion sequence, which then undergoes reductive elimination to provide β- or even long-range functionalized molecules. As mentioned in bibliographic part, based on this ligand-controlled strategy, our group has successfully realized a series of β- or long-range functionalization using enolates or organozinc compounds as nucleophiles.

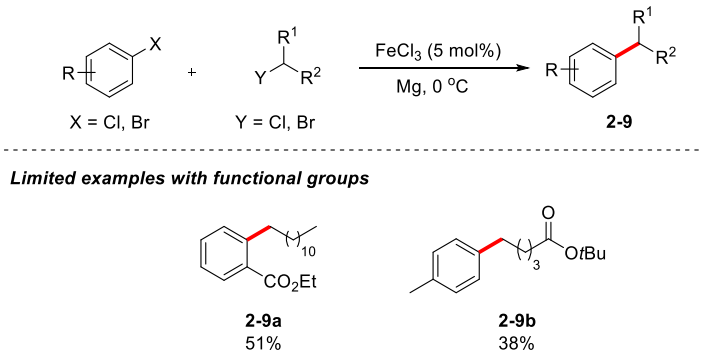


Scheme 2.2. Remote C-H functionalization by migrative cross-coupling reactions

1.2 Barbier-type reactions

The Barbier reaction is an organic reaction between an alkyl halide and a carbonyl group as an electrophilic substrate in the presence of a metal, such as magnesium, aluminium, zinc, indium, tin, or its salts.[55] The reaction is similar to the Grignard reaction but the crucial difference is that the Barbier reaction is a one-pot synthesis, since the organometallic species used in this reaction are generated *in-situ*. This method provides a simple and step-economy way for cross-coupling reactions, avoiding the handle of air- or moisture-sensitive organometallic species.

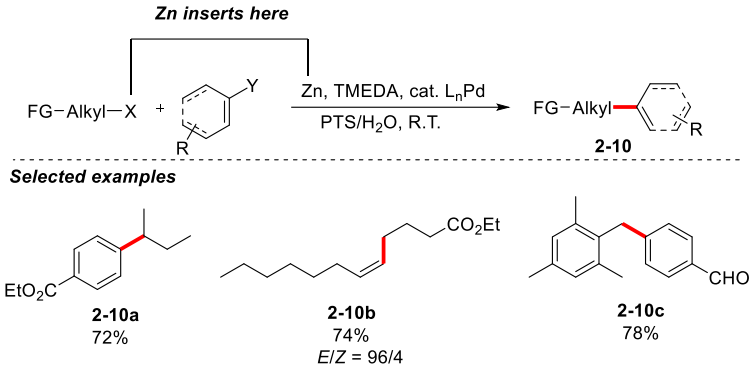
In 2009, von Wangelin and co-workers reported a new, operationally simple and one-pot iron-catalyzed C(sp^2)-C(sp^3) cross-coupling with *in-situ* generated Grignard reagent (Scheme 2.3).[56] Due to the nature of Grignard reagents, however, there is limited tolerance of functional groups in either coupling partners.



Scheme 2.3. Domino iron catalysis enables direct aryl–alkyl cross-coupling

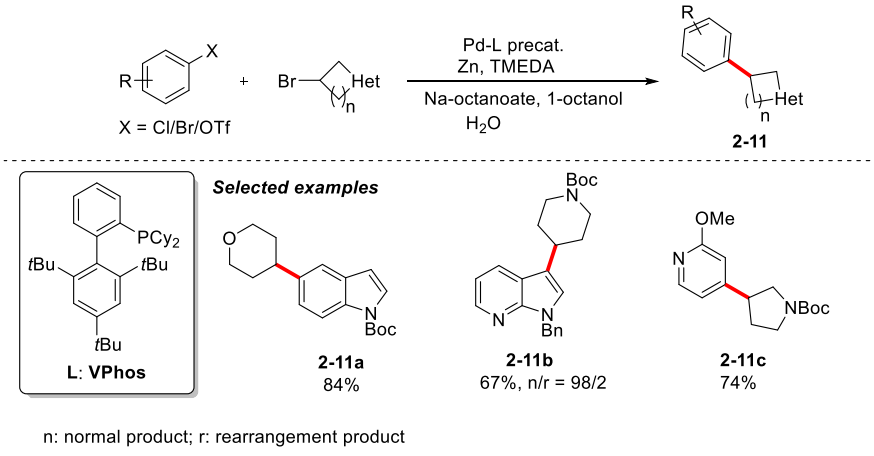
Later, the direct Barbier-Negishi cross-couplings were reported by the Lipshutz group, which utilized water as the solvent and a diamine as an additive, either in the presence of a surfactant

(**2-10a**, **2-10b**) or under ‘‘on water’’ (**2-10c**) conditions (Scheme 2.4).[57] Nevertheless, one drawback of this approach is that competitive reduction of the aryl halides often occurred and a significant excess of the alkyl halide was required to suppress this side reaction.



Scheme 2.4. Barbier-Negishi cross-couplings developed by the Lipshutz group

An improved catalytic system developed by Buchwald and co-workers enables the rapid construction of a broad range of cyclic alkylated scaffolds from alkylzinc reagents generated *in-situ* (Scheme 2.5).[58] They found that the simple combination of octanoic acid/sodium octanoate is an efficient surfactant system for this micelle-enhanced Negishi cross-coupling, allowing the C(sp^3)-C(sp^2) cross-coupling reactions to occur with a broad spectrum of electronically differentiated (hetero)aryl halides and as little as 1.5 equivalents of a variety of aliphatic heterocyclic bromides.

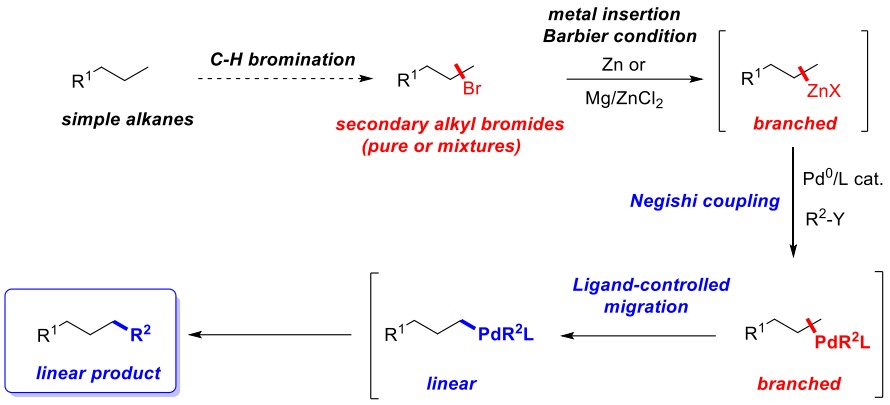


Scheme 2.5. An improved Barbier-Negishi coupling developed by the Buchwald group

1.3 Research plan

Secondary alkyl bromides are simple and readily available motifs, which can be easily generated by the bromination of abundant feedstocks, such as alkenes, alcohols or even

alkanes.[59] Therefore, in this part, we would like to extend the migrative cross-couplings to either pure or non-useful mixtures of secondary alkyl bromides, expecting to achieve terminal-selective functionalization of alkyl chains regioconvergently (Scheme 2.6). In addition, Barbier conditions with organozincs generated *in-situ* will be utilized to maximize the overall step economy.



Scheme 2.6. Overview of research plan

2. Migrative Barbier-Negishi cross-couplings

2.1 Optimization of the reaction conditions

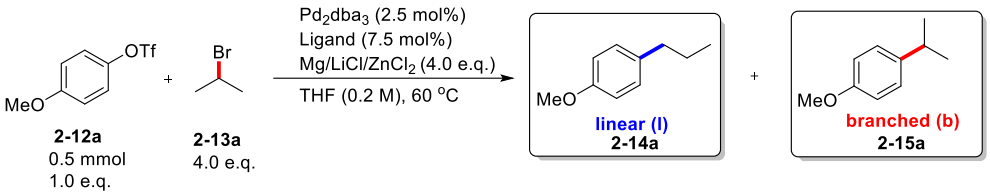
2.1.1 Ligands effect

Preliminary work on this topic in our group was reported by Dr. Anne-Sophie Goutierre in her Ph.D. thesis.[60] With the aid of a flexible phosphine ligand, the proposed reaction was demonstrated to be feasible to achieve the terminal functionalization of alkyl chains using preformed secondary alkylzincs as the coupling partners. Nevertheless, the developed reaction was limited to a narrow scope and the preparation of organozincs from alkyl bromides met with difficulties due to the zinc insertion problems in some cases. Therefore, at the outset of our studies, we wanted to seek for suitable and practical conditions for the generation and cross-coupling of alkylzinc compounds. After extensive investigations, Dr. Stéphanie Dupuy developed the Barbier conditions to achieve that goal.

To avoid competitive metal insertion, aryl triflates were chosen as electrophiles, and therefore they should show orthogonal reactivity to alkyl halides.[61] Previous studies demonstrated that ligands play an important role in controlling the site-selectivity, hence, we started to investigate the reaction of 2-Br propane with a library of in-house ligands under Barbier

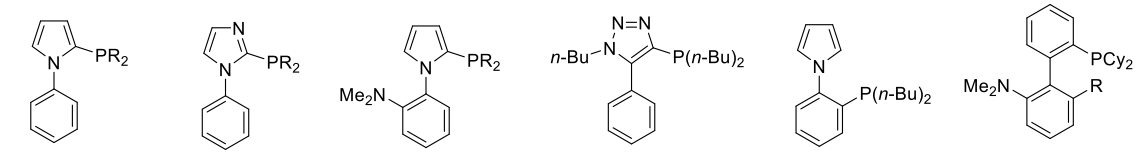
conditions where the organozinc reagent was generated *in-situ* by magnesium insertion and transmetallation with $ZnCl_2$ (Table 2.1).[62]

Table 2.1. Effect of ligands in migrative Barbier-Negishi couplings



Entry	Ligand	Conversion (%)[a]	l/b[a]	Yield of **2-14a** (%)[a]
1	**L^2**	35	42/58	12
2	**L^3**	-	-	<10
3	**L^4**	93	78/22	41
4	**L^5**	-	-	<10
5	**L^6**	100	92/8	52
6	**L^7**	97	93/7	47
7	**L^8**	100	95/5	32
8	**L^9**	96	33/67	28
9	**L^{10}**	46	22/78	12
10	**L^{11}**	74	88/12	22
11	**L^{12}**	100	92/8	42
12	**CPhos**	100	<2/98	84[b]
13	**DavePhos**	100	4/96	83[b]

[a] Measured by GC-MS with tetradecane as an internal standard; [b] Isolated yield of branched product **2-15a**.



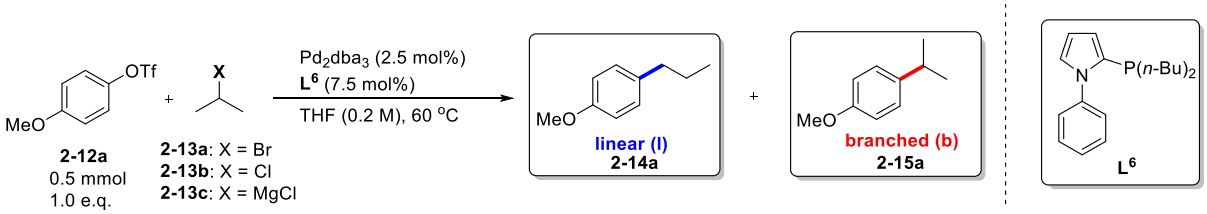
As depicted in Table 2.1, ligands indeed have a remarkable influence on the selectivity and reactivity. Among these ligands, the phenyl-pyrrole-based phosphine ligand **L^6** gave the best result in terms of both linear selectivity and yield (entry 5). The unique property of **L^6** could be explained by the high level of flexibility of this ligand due to the phenyl-pyrrole backbone and also the linear group *n*-Bu at the phosphorus atom. On the contrary, rigid and bulky

ligands, such as CPhos[29a] and DavePhos[63], gave a completely inversed selectivity, affording the branched product **2-15a** in good yields (entry 12 & entry 13). These results highly correlate with the ‘‘ligands effect’’ in the cross-coupling reactions discussed in Chapter 1.

2.1.2 Optimization of other reaction parameters

With the best ligand in hand, we next further optimized the other reaction parameters. Changing 2-bromo propane **2-13a** to 2-chloro propane **2-13b** resulted in similar results in the presence or absence of $ZnCl_2$ (entry 1 VS. entry 2, entry 3 VS. entry 4). A control experiment with commercially available Grignard reagent **2-13c** also gave a similar linear selectivity and comparable yield of **2-14a** (entry 5). Further control experiments disclosed that $ZnCl_2$ is crucial to achieve a better result, especially for substrates with functional groups like ester (entry 6 VS. entry 7). Organozinc reagent generated *in-situ* from the mixture of Mg, LiCl and $ZnCl_2$ is more efficient than from the mixture of zinc dust and LiCl, since a low yield was obtained when zinc dust was engaged in the reaction mixture (entry 9).[64] Final optimization showed that the organozinc reagent generated *in-situ* could be reduced to 2.0 equiv. (entry 8) and the reaction worked well even with 2.5 mol% palladium catalysts (entry 10), but a lower yield was obtained with 1.25 mol% (entry 11). In the end, the optimal condition is: **2-13a**/ Mg/LiCl/$ZnCl_2$ (2 equiv.), 1.25 mol% Pd_2dba_3 and 2.5 mol% **L^6**, 60 ^oC, 16 h, giving rise to the linear product **2-14a** in 92% selectivity and 80% isolated yield of mixture of linear/branched products.

Table 2.2. Optimization of other reaction parameters



Entry	Organometallic reagent (equiv.)	l/b[a]	Yield of **2-14a** (%)[a]
1	**2-13a**/Mg/LiCl/$ZnCl_2$ (4)	92/8	52
2	**2-13b**/Mg/LiCl/$ZnCl_2$ (4)	92/8	45
3	**2-13a**/Mg/LiCl (4)	87/13	52
4	**2-13b**/Mg/LiCl (4)	89/11	62
5	**2-13c**/LiCl (1.3)	88/12	72
6[b]	**2-13a**/Mg/LiCl (4)	63/37	<10

7[b]	**2-13a**/Mg/LiCl/$ZnCl_2$ (4)	87/13	(76)[c]
8	**2-13a**/Mg/LiCl/$ZnCl_2$ (2)	92/8	82 (83)[c]
9	**2-13a**/Zn/LiCl (2)	90/10	18
10[d]	**2-13a**/Mg/LiCl/$ZnCl_2$ (2)	92/8	76 (80)[c]
11[e]	**2-13a**/Mg/LiCl/$ZnCl_2$ (2)	92/8	66 (64)[c]

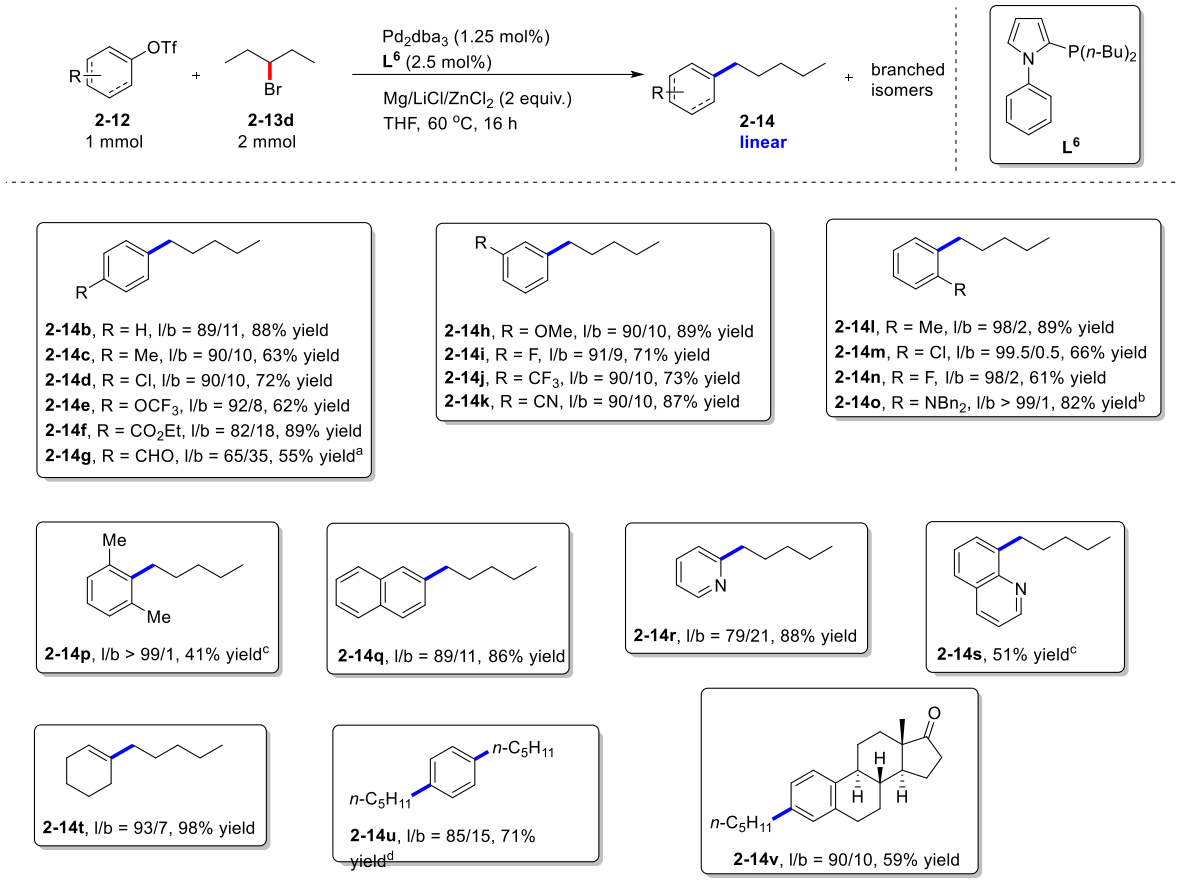
[a] Measured by GC-MS with tetradecane as an internal standard; [b] 4-$CO_2EtC_6H_4OTf$ was used; [c] isolated yield of mixture; [d] Catalyst loading: 1.25 mol% Pd_2dba_3/2.5 mol% **L**^{6}; [e] 0.625 mol% Pd_2dba_3/1.25 mol% **L**^{6}.

2.2 Scope and limitations of migrative Barbier-Negishi couplings

2.2.1 Coupling of aryl/alkenyl triflates with 3-bromopentane

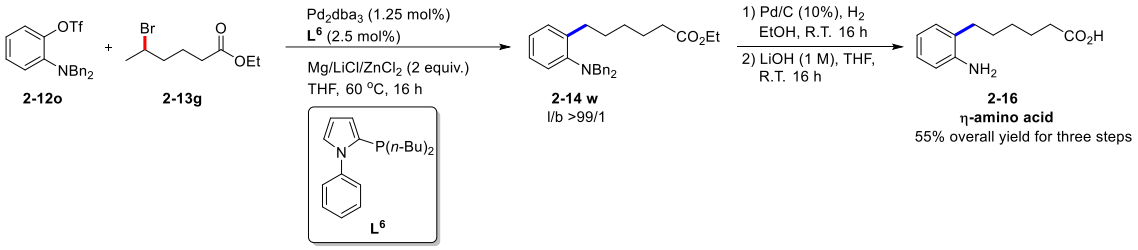
Under the optimal reaction conditions, the scope and limitations of this migrative Barbier-Negishi cross-coupling reaction with regard to different triflates were then investigated by Dr. Stéphanie Dupuy. In general, the reaction was found to be compatible with a wide range of triflates, giving rise to the corresponding linear products in good yields and selectivities (Scheme 2.7). Functional groups, such as ester (**2-14f**), nitrile (**2-14k**) and even more electrophilic aldehyde (**2-14g**) were well tolerated due to the nature of Negishi cross-couplings. As expected, *ortho*-substituted aromatic triflates gave exclusively the linear products, which is consistent with our previous studies (**2-14l** to **2-14o**).[43, 46-48, 51-52] A control experiment with the substrate **2-12o** was conducted using CPhos as the ligand, showing that the selectivity is controlled by both the ligand and substrate (the selectivity for **2-14o**: l/b >99/1 with **L**^{6} and 73/27 with CPhos).

Heteroaromatic triflate (**2-12r**) is also possible under the established conditions, albeit with a relatively lower linear selectivity. Cyclic alkene triflate is another interesting example, since the desired linear product (**2-14t**) was obtained in 98% yield and 93% selectivity. We were pleased to find that the double migrative cross-coupling also gave a good result (**2-14u**, 71% yield, l/b 85/15). Moreover, the developed conditions could be even applied to a more complex example-estrone derived triflate with a free ketone (**2-12v**), thus further demonstrating the generality of our protocol. Of note, simply combination of a triflate and a secondary alkyl bromide enabled the synthesis of η-amino acid **2-16** in 55% yield over a three-step sequence: migrative Barbier-Negishi coupling/hydrogenation/saponification (Scheme 2.8).



Note: The linear/branched ratio was measured by GC-MS; Yield refers to the yield of the isolated mixture of linear/branched products.
[a] Using 4 equiv $ZnCl_2$; [b] With **CPhos** as the ligand, the l/b ratio was 73:27; [c] Yield of the pure linear product; in this case the l/b ratio could not be determined; [d] Using 2.5 mol% Pd_2dba_3/5 mol% **L6**.

Scheme 2.7. Scope and limitations with respect to aryl/alkenyl triflates

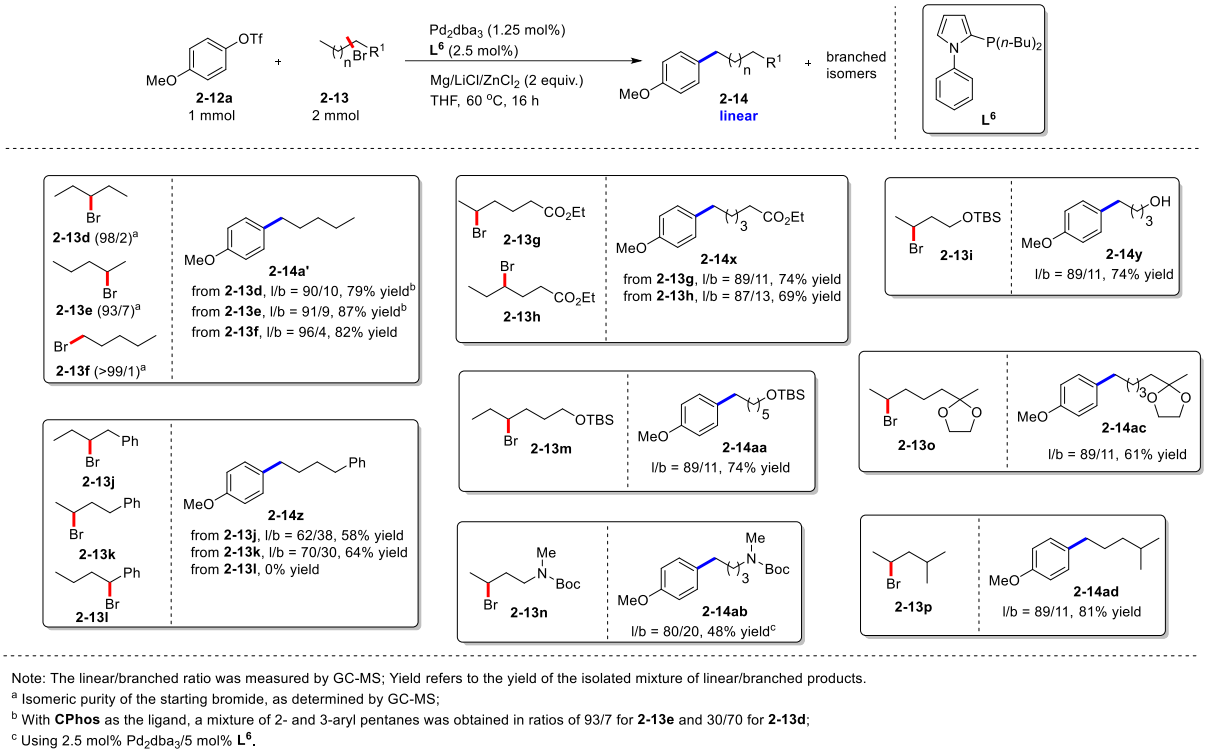


Scheme 2.8. Application of migrative Barbier-Negishi coupling to the synthesis of η-amino acid

2.2.2 Coupling of 4-methoxyphenyl trifluoromethanesulfonate with secondary alkyl bromides

Next, the coupling of 4-methoxyphenyl trifluoromethanesulfonate **2-12a** with various secondary alkyl bromides was studied. Due to the nature of organozinc reagent, various functional groups, such as esters (**2-13g**, **2-13h**), TBS-protected alcohols (**2-13i**, **2-13m**), protected amine (**2-13n**) and acetal (**2-13o**), were all well tolerated under the Barbier

conditions. In addition, we were pleased to find that the reaction regioconvergently afforded mainly the linear product in all cases, no matter where the bromine atom is on the alkyl chain. Nevertheless, this is not the same case for the isomeric bromides containing a phenyl group, since significantly different selectivities for the linear product were observed and bromide **2-13l** did not give any coupling product. These results could be attributed to the presence of a benzyl position, which disfavours the palladium migration and C-C reductive elimination. Interestingly, when bromide **2-13p** was engaged in the current Barbier conditions, compound **2-14ad** was obtained as the only linear product. No trace of the other possible linear product was observed from GC-MS, suggesting that branched motif could block palladium migration along the alkyl chain.



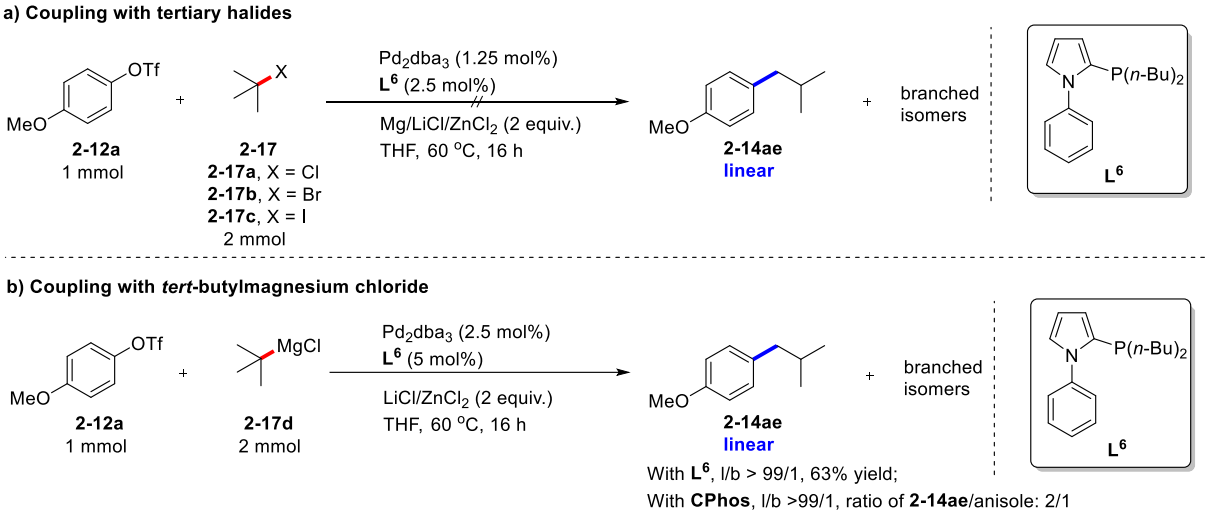
Note: The linear/branched ratio was measured by GC-MS; Yield refers to the yield of the isolated mixture of linear/branched products.
[a] Isomeric purity of the starting bromide, as determined by GC-MS;
[b] With **CPhos** as the ligand, a mixture of 2- and 3-aryl pentanes was obtained in ratios of 93/7 for **2-13e** and 30/70 for **2-13d**;
[c] Using 2.5 mol% Pd_2dba_3/5 mol% **L6**.

Scheme 2.9. Scope and limitations with respect to secondary alkyl bromides

2.2.3 Coupling of 4-methoxyphenyl trifluoromethanesulfonate with tertiary alkyl substrates

Besides the secondary alkyl bromides, tertiary alkyl halides were also examined to see the generality of this reaction. Unfortunately, the desired product was not obtained in all cases (Scheme 2.10a). We assumed that the lack of reactivity might originate from the magnesium insertion step, which is known to be quite slow to tertiary halides.[65] Therefore, the commercially available *tert*-butylmagnesium chloride was engaged in the reaction instead,

and we were delighted to find that the reaction worked quite well, affording the desired linear product in 63% isolated yield with 100% linear selectivity (Scheme 2.10b). Control experiment with CPhos was conducted, leading to the complete linear product as well. However, the only difference between **L^6** and CPhos is that significant amount of reduction product anisole was produced when CPhos was used, which is difficult for the purification by column chromatography (Scheme 2.10b). Consequently, **L^6** continued to be the best ligand for the tertiary substrates.

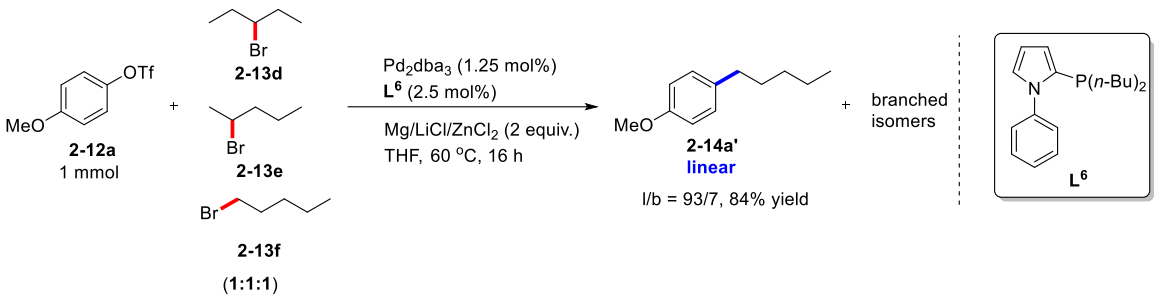


Scheme 2.10. Coupling with tertiary halides

2.3 Two-step linear-selective functionalization of alkanes

2.3.1 Proof-of-concept

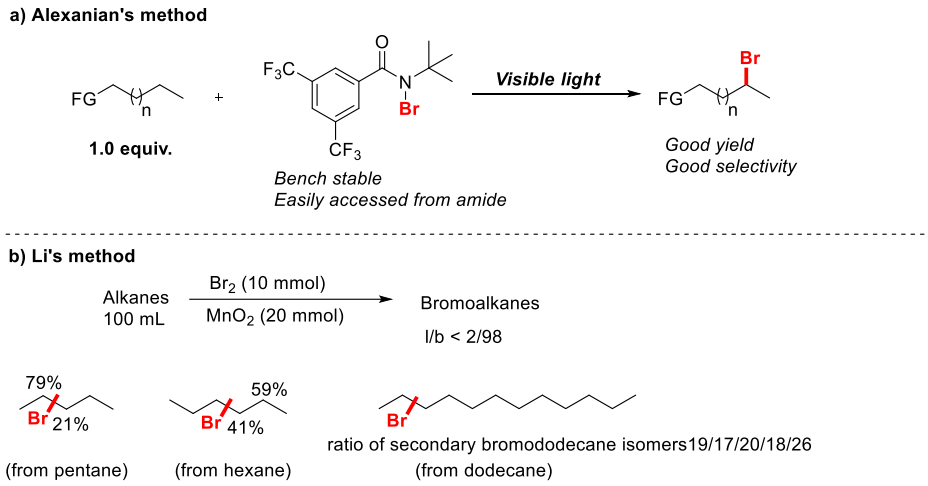
As observed from the scope study with different secondary alkyl bromides, linear products were mainly obtained in a regioconvergent manner despite of the position of bromine atom on the alkyl chain. To further examine the possibility of regioconvergent cross-coupling with mixtures of alkyl bromides prepared from the non-selective bromination of simple alkanes, a proof-of-concept experiment was firstly performed using an equimolar mixture of bromopentanes. As expected, the reaction gave a similar result in terms of both yield and selectivity, compared to the results with isolated bromopentanes (Scheme 2.11). This result suggested that the same principle could be applied to the regioconvergent coupling of mixtures of alkyl bromides with various molar compositions.



Scheme 2.11. A proof-of-concept experiment on the regioconvergent cross-coupling

2.3.2 Radical bromination of alkanes

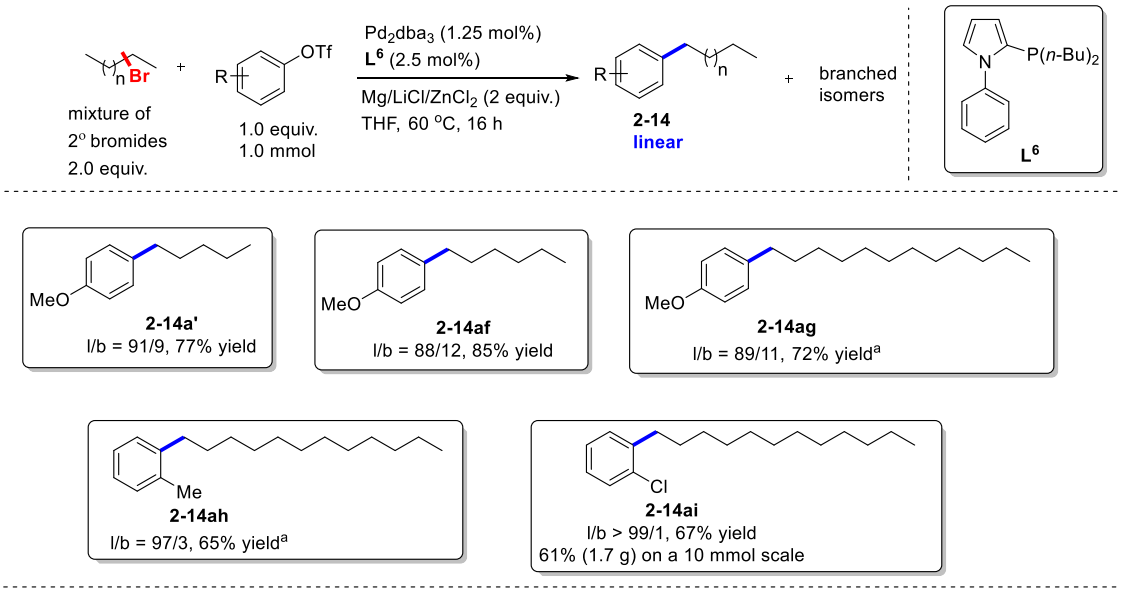
At the beginning of this project, we aimed to find a practical method to prepare the mixtures of secondary alkyl bromides. In 2014, Alexanian group developed a site-selective, intermolecular bromination of unactivated, aliphatic C−H bonds using *N*-bromoamides and visible light (Scheme 2.12a).[66] While this radical-mediated process allows the utility of hydrocarbons as limiting reagent in all examples, limitations still exists, especially when we want to prepare the mixtures of alkyl bromides on large scale. Although great efforts were made on this part for a long time, we still could not get satisfying result. After extensive exploring work, in the end, the desired mixtures could be obtained using the method developed by Li and co-workers,[67] which is operationally simple and could be performed well even on large scale. Nevertheless, the only problem is that this methodology was limited to simple alkanes. With this approach, we were able to obtain the following three mixtures of alkyl bromides starting from *n*-pentane, *n*-hexane and *n*-dodecane (Scheme 2.12b).



Scheme 2.12. Radical bromination of alkanes

2.3.3 Linear-selective functionalization of alkanes from mixtures of secondary alkyl bromides

With the mixtures of alkyl bromides in hand, we then examined the regioconvergent cross-couplings with various electrophiles. As shown in Scheme 2.13, excellent results were observed with these three mixtures, furnishing the linear products with good to excellent selectivities, depending on the aryl triflates used. Moreover, the regioconvergent coupling could be performed on a 10 mmol scale without a significant decrease in efficiency, which further demonstrated the practicality of our protocol. Therefore, the terminal-selective functionalization of simple alkanes could be achieved with a sequence of non-selective bromination/migrative Barbier-Negishi cross-couplings.

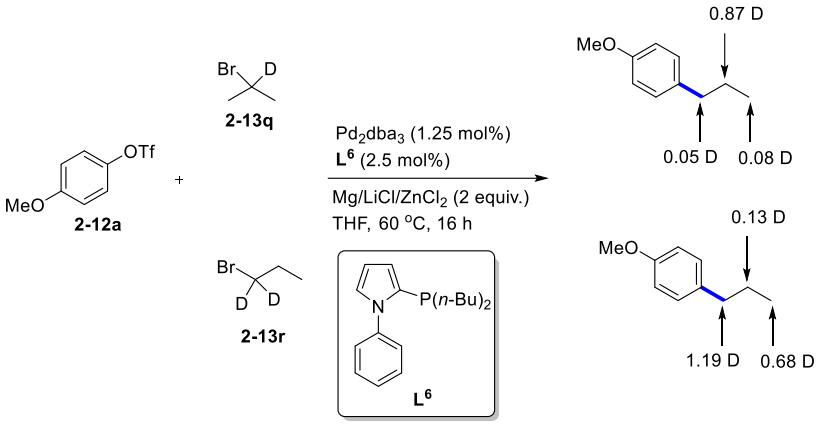


Note: The linear/branched ratio was measured by GC-MS; Yield refers to the yield of the isolated mixture of linear/branched products.
[a] Using 2.5 mol% Pd_2dba_3/5 mol% **L**^{6}.

Scheme 2.13. Regioconvergent cross-coupling with mixtures of bromoalkanes

2.4 Deuterium labelling experiments

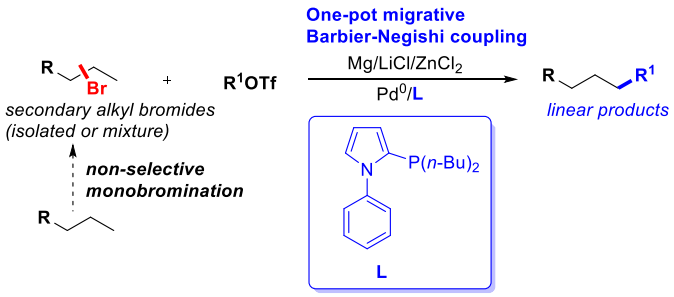
In order to gain a better understanding of the reaction pathway, deuterated 1- and 2-bromopropane were engaged in this Barbier-Negishi cross-coupling reaction (Scheme 2.14). The pronounced deuterium scrambling observed with **2-13r** shows that the palladium migration is reversible along the alkyl chain. Additionally, the unequal deuterium distribution on the three carbons of the propyl chain observed from both deuterated 1- and 2-bromopropane likely reflects the intramolecular isotope effect associated with the faster β-H VS. β-D elimination from the intermediate organopalladium species.[68]



Scheme 2.14. Experiments with deuterated substrates.

3. Conclusion

To conclude, we have extended the ligand-controlled palladium migration to simple and commercially available secondary alkyl bromides. Under practical Barbier-type conditions involving magnesium insertion and transmetallation with $ZnCl_2$, a series of linear arylated alkanes could be obtained in a regioconvergent manner with good to excellent linear/branched selectivities, thanks to the use of a suitable phosphine ligand. Moreover, this strategy could be coupled to a non-selective radical monobromination process, which allowed the terminal-selective functionalization of simple alkanes in just two steps.



Scheme 2.15. Overview of the palladium-catalyzed migrative Barbier-Negishi cross-coupling reaction

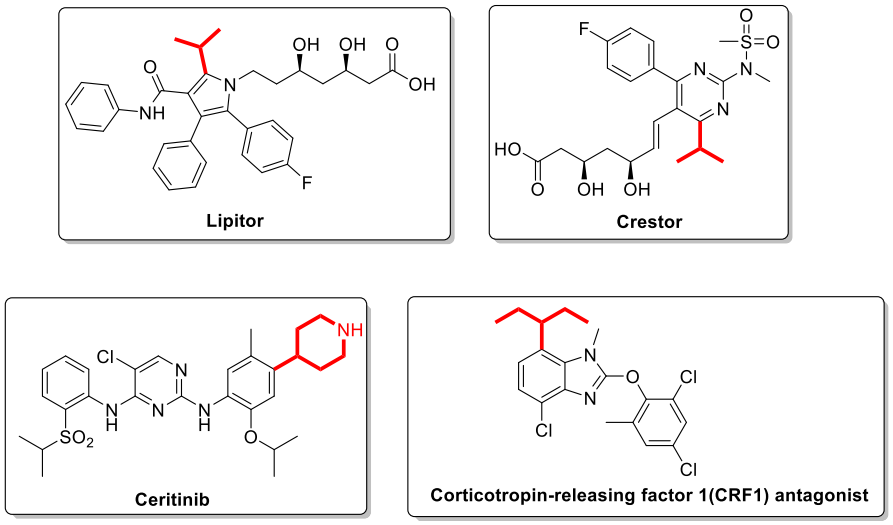
After our work was published, the migrative coupling of alkyl bromides has witnessed significant developments. These include using cheap and abundant nickel catalysis[69] and also photocatalysis[70]. We believe that these unconventional methodologies will represent powerful alternatives to existing methods for promoting functionalization of the remote reaction site.[71]

Chapter 3

Direct Barbier-Negishi coupling of secondary alkyl bromides with aryl and alkenyl triflates and nonaflates

1. Introduction and research plan

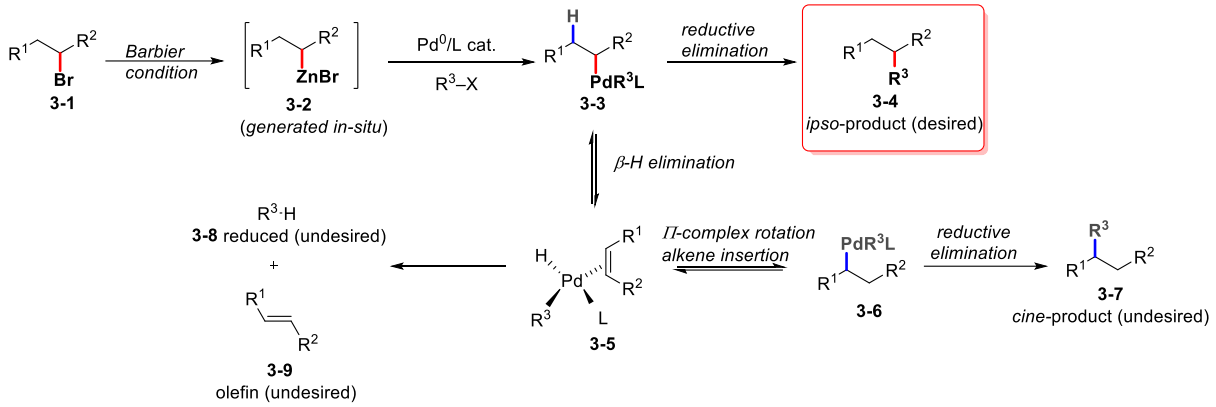
Alkyl groups, especially secondary alkyl ones, are important and ubiquitous motifs found in numerous pharmaceuticals and natural products, such as the top ten selling drugs Lipitor and Crestor (Scheme 3.1).[72] Consequently, extensive studies have been devoted to the direct and rapid construction of $C(sp^2)$-$C(sp^3)$ bonds in both laboratory and industry. Among all the methods established, direct Negishi cross-coupling reaction has been demonstrated to be a reliable and practical approach to form $C(sp^2)$-$C(sp^3)$ bonds. Although great achievements have been made in this area, two main challenges still exist: the requirement of preformed organozinc compounds and most importantly the site-selectivity issue due to *β*-hydride elimination.



Scheme 3.1. Examples of pharmaceuticals containing a secondary alkyl group

To overcome the site-selectivity problem in $C(sp^2)$-$C(sp^3)$ cross-couplings, the development of catalyst system to speed reductive elimination (from **3-3** to **3-4**) while suppressing the competitive *β*-hydride elimination (from **3-3** to **3-5**) is the most important task. In this regard, various ligands and catalyst systems have been developed to inhibit the migratory pathway (from **3-3** to **3-7**) and facilitate the formation of direct cross-coupling product **3-4**. However, in all these cases, the moisture-sensitive organozinc reagents have to be prepared prior to the coupling step. On the other hand, as described in the introduction part of Chapter 2, Lipshutz[57] and Buchwald[58] groups independently reported the Barbier-Negishi coupling conditions, which avoid the preformation of organozinc species. Recently, our group applied the water-free Barbier conditions to the terminal-selective functionalization of alkyl chains based on the migrative cross-coupling strategy.[73] Following the interests in the field of

‘‘ligand-controlled selectivity’’ in palladium-mediated cross-coupling reactions, in this part, we would like to favour the direct coupling product **3-4** by examining and designing bulky ligands, expecting to develop a mild and highly selective C(sp^2)-C(sp^3) Negishi cross-coupling.



Scheme 3.2. Barbier-Negishi coupling of secondary alkyl bromides

2. Direct Barbier-Negishi coupling of secondary alkyl bromides with aryl and alkenyl triflates and nonaflates

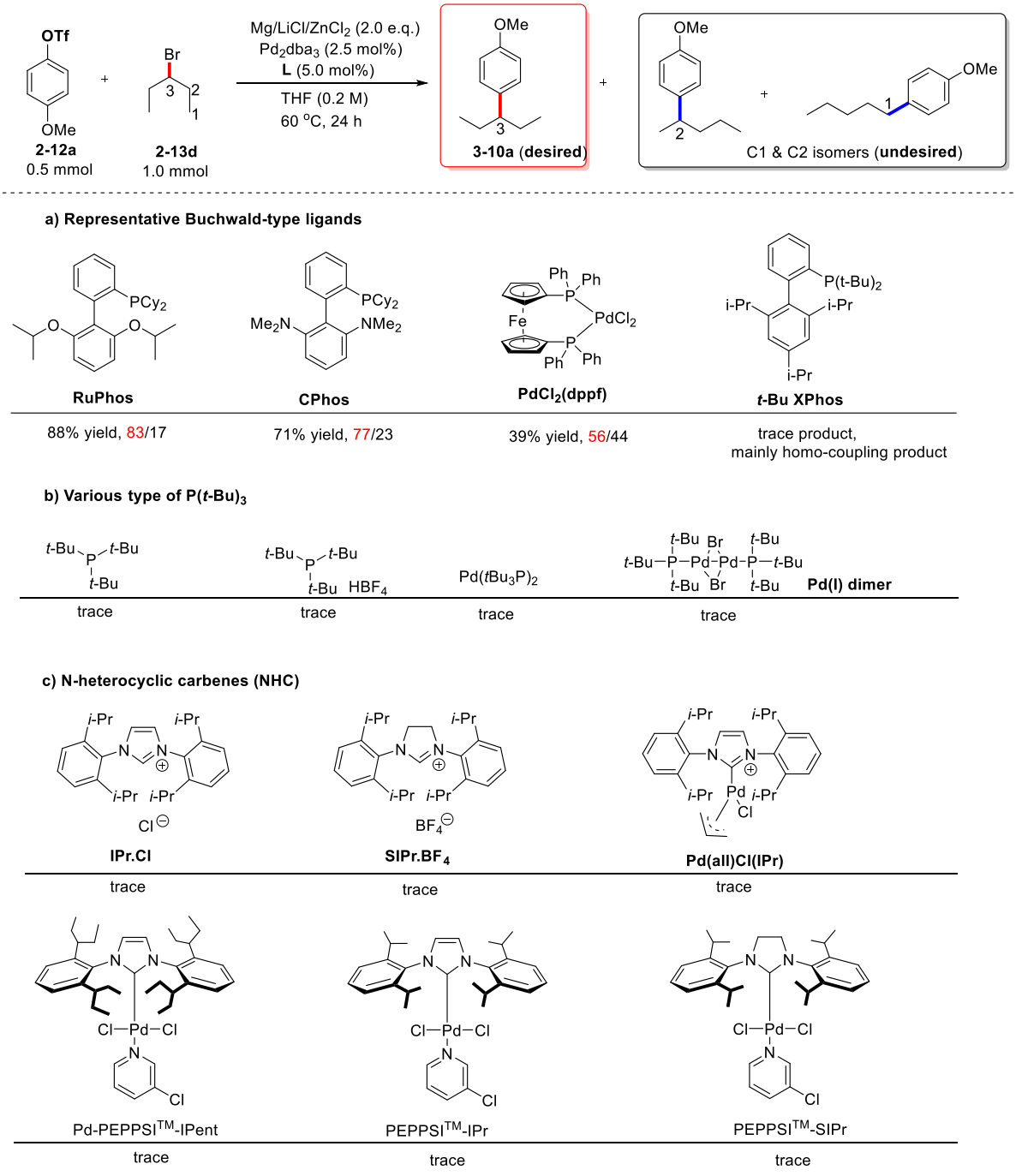
2.1 Optimization of the reaction conditions

2.1.1 Initial results using commercially available and previously reported ligands

Our initial efforts to achieve the more challenging direct Barbier-Negishi cross-couplings using various reported or commercially available ligands under palladium catalysis did not give satisfying results. All the tested phosphine ligands gave low to moderate selectivities in the Barbier-Negishi reaction of aryl triflate **2-12a** and 3-bromopentane (Scheme 3.3a). CPhos,[29] which was shown to be completely selective formation of the direct coupling product in our previously studied Barbier conditions with 2-bromopropane,[73] led to only 77% selectivity in the system of 3-bromopentane. Other types of Buchwald ligands were further examined. Whereas RuPhos[74] afforded a slightly higher direct selectivity (83/17) and a better yield (88%), *t*-Bu XPhos[75] mainly delivered the homocoupling product of **2-12a**. The use of $PdCl_2$(dppf)[26] provided low conversion and poor selectivity for the direct product.

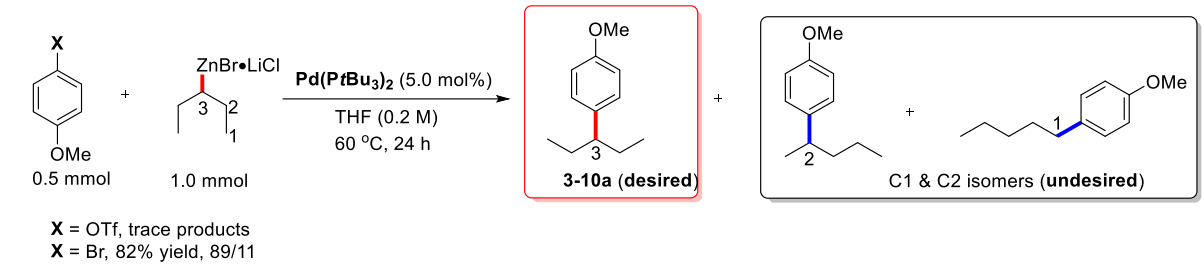
In addition, various types of tri-*tert*-butylphosphine[27, 76] were examined. To our surprise, the reactions failed to give any coupling product with these ligands (Scheme 3.3b). The unexpected result could be attributed to the problem of triflates used as the coupling partner.[77]

Control experiment was then conducted with the preformed organozinc compound. No products were observed when triflate was used in the presence of $Pd(PtBu_3)_2$, however, the reaction gave the desired *ipso*-product in 82% GC yield and 89% selectivity when 4-methoxyphenyl bromide was engaged in(Scheme 3.4).



Note: Yield described was determined by GC analysis using dodecane as an internal standard;
Selectivity was determined by GC ratios of **3-10a**/sum of the C1 and C2 isomers

Scheme 3.3. Test of various catalyst systems in the direct Barbier-Negishi coupling of 3-bromopentane

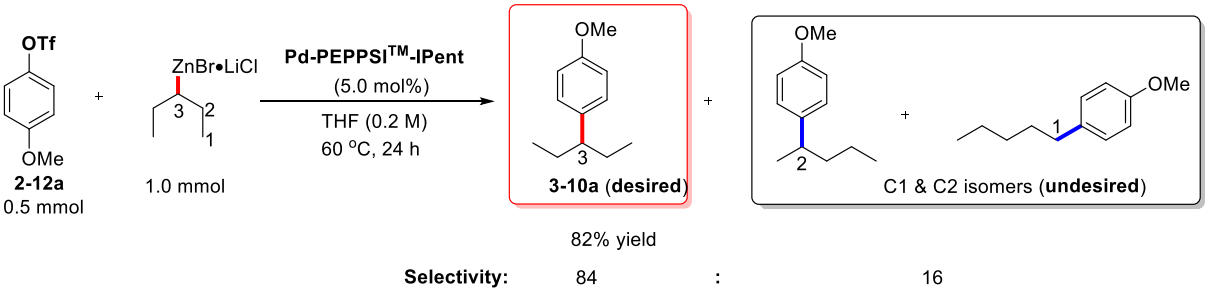


X = OTf, trace products
X = Br, 82% yield, 89/11

Note: Yield described was determined by GC analysis using dodecane as an internal standard;
Selectivity was determined by GC ratios of **3-10a**/sum of the C1 and C2 isomers

Scheme 3.4. Control experiments with $Pd(PtBu_3)_2$ as the catalyst system

Another very important type of ligands-*N*-heterocyclic carbenes (NHCs) were not compatible with Barbier conditions. In all cases, no coupling products were observed no matter what type of NHC was used (Scheme 3.3c). The PEPPSI-type complexes developed by the Organ group,[39] which have found great applications in the cross-coupling reactions, also failed under the Barbier conditions. However, the control experiment with the corresponding preformed organozinc reagent showed a restored activity and moderate selectivity (84/16) (Scheme 3.5).



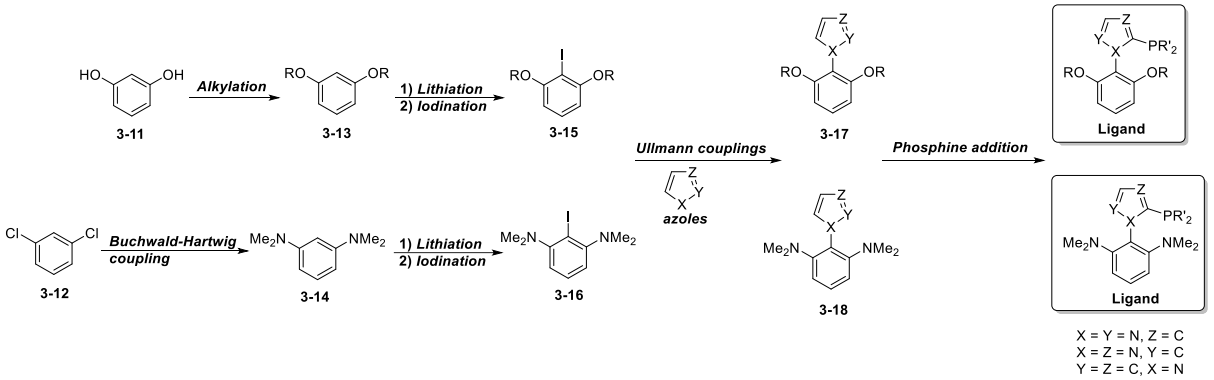
Note: Yield described was determined by GC analysis using dodecane as an internal standard;
Selectivity was determined by GC ratios of **3-10a**/sum of the C1 and C2 isomers

Scheme 3.5. Control experiment with the preformed organozinc species in the presence of Pd-PEPPSI™-IPent

2.1.2 Design and development of new phosphine ligands

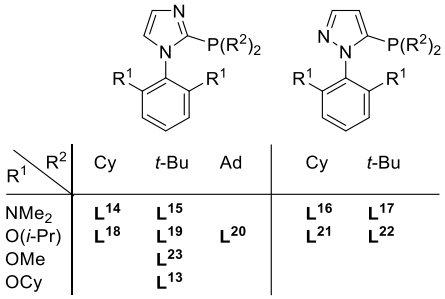
Since no satisfying results were obtained, we aimed to design a series of sterically demanding, azole-based phosphine ligands based on the previous studies from our and other research groups. Azole-based phosphine ligands were firstly introduced by Beller and co-workers and have found a wide range of applications in different cross-coupling reactions.[78] Moreover, these azole-based analogues performed better than the conventional biaryl phosphine ligands in some cases. On the other hand, Buchwald group has demonstrated that the modification on the lower aromatic ring with electron-rich substituents, such as OMe, O*i*Pr and NMe_2, has a profound effect on both activity and selectivity.[79]

With these considerations in mind, two different families of rigid and bulky azole-based phosphine ligands were designed and synthesized from commercially available and easily accessed starting materials. The synthetic routes are shown below (Scheme 3.6).



Scheme 3.6. Proposed synthetic routes for bulky azole-based phosphine ligands

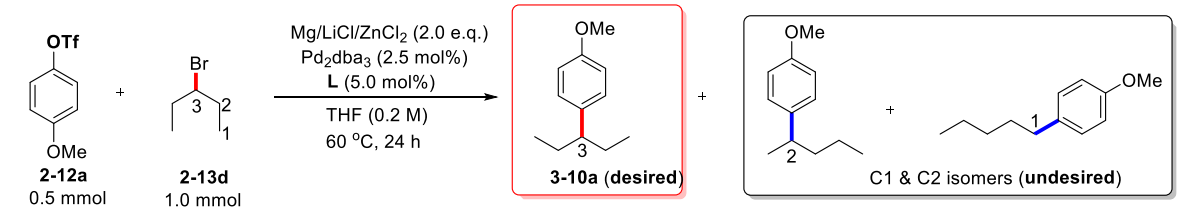
The Master student Fadri Christoffel, supervised by Dr. Stéphanie Dupuy, initiated the project and contributed to some of the ligands synthesis.[80] According to these routes, totally eleven new azole-based bulky phosphine ligands were obtained (Scheme 3.7). However, efforts to make the corresponding pyrrole-based bulky phosphines failed, although different procedures were tried.

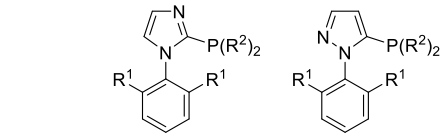


Scheme 3.7. List of newly synthesized bulky azole-based phosphine ligands

2.1.3 Test of new ligands in the direct Barbier-Negishi coupling

Table 3.1. Effect of newly synthesized bulky phosphine ligands in the direct Barbier-Negishi coupling





R^1 \ R^2	Cy	*t*-Bu	Ad	Cy	*t*-Bu
NMe_2	**L**^{14}	**L**^{15}		**L**^{16}	**L**^{17}
O(*i*-Pr)	**L**^{18}	**L**^{19}	**L**^{20}	**L**^{21}	**L**^{22}
OMe		**L**^{23}			
OCy		**L**^{13}			

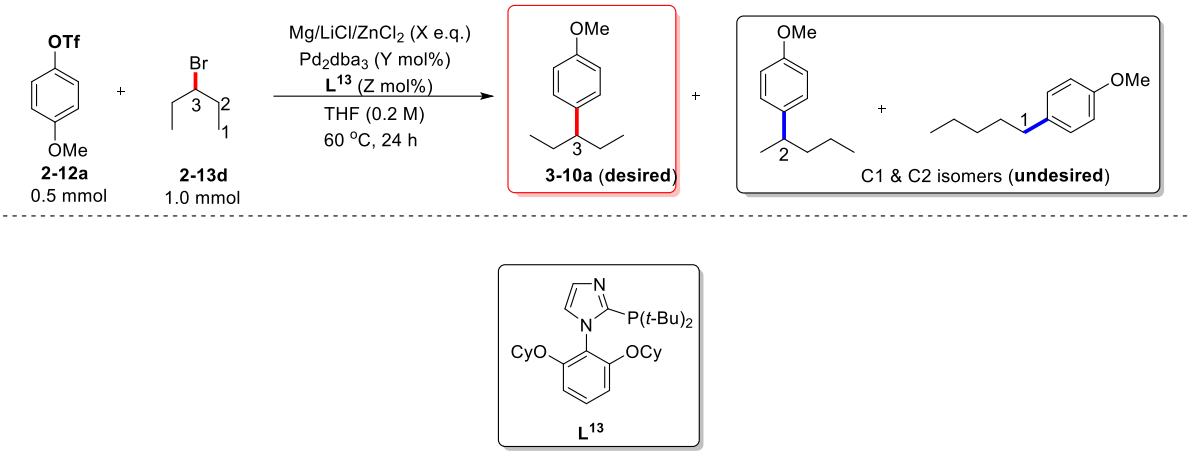
Entry	**L**	Yield (%) [a]	Selectivity[b]
1	**L**^{13}	83	93/7
2	**L**^{14}	<5	-
3	**L**^{15}	41	93/7
4	**L**^{16}	20	64/36
5	**L**^{17}	11	90/10
6	**L**^{18}	<5	-
7	**L**^{19}	73	93/7
8	**L**^{20}	61	94/6
9	**L**^{21}	61	77/23
10	**L**^{22}	18	81/19
11	**L**^{23}	56	92/8
12[c]	**L**^{13}	76	95/5

[a] Yields of **3-10a** were determined by GC analysis using dodecane as an internal standard; [b] GC ratios of **3-10a**/sum of the C1 & C2 isomers; [c] Performed using the preformed organozinc halide under otherwise identical reaction conditions.

With the newly synthesized azole-based phosphine ligands in hand, their reactivities and selectivities were then examined in the direct Barbier-Negishi coupling of 4-methoxyphenyl trifluoromethanesulfonate **2-12a** with 3-bromo pentane **2-13d**. The CPhos analogues containing an imidazole or a pyrazole only gave a moderate reactivity, but the selectivity for the direct coupling product was greatly improved when the phosphorus atom has a di-substituted *t*-Bu group (entries 2-5). Delightedly, the RuPhos analogues showed superior results considering both reactivity and selectivity (entries 6-11). As seen from Table 3.1, *tert*-butyl substitutents on the phosphorus atom provided optimal reactivity and selectivity compared to cyclohexyl and adamantly groups (entries 6-8). The imidazole ring is better than the corresponding pyrazole (entries 19 & 22). In addition, the cyclohexyloxy group on the *ortho*-positions of lower aromatic ring gave rise to the desired branched product in a higher yield than the corresponding methoxy and isopropoxy groups (entries 1, 7 & 11). We were quite surprised to observe that the reaction failed to give any products when the substituents on the phosphorus atom were replaced by two cyclohexyl groups (entry 2 VS. entry 3, entry 6 VS. entry 7). So far, no satisfying explanation could be given on the huge difference between cyclohexyl and *tert*-butyl groups. A control experiment using **L**^{13} and the prepared organozinc halide showed that this ligand works equally well under both normal conditions and Barbier conditions (entry 12).

2.1.4 Optimization of other reaction parameters

Table 3.2. Optimization of other reaction parameters



entry	Temp. (°C)	X	Y	Z	Yield (%)[a]	Selectivity[b]
1	60	2.0	2.5	5.0	83	93/7
2	60	2.0	1.25	2.5	56	93/7
3	60	1.5	2.5	5.0	82	94/6
4[c]	25	1.5	2.5	5.0	(90)[d]	94/6

[a] Yields of **3-10a** were determined by GC analysis using dodecane as an internal standard; [b] GC ratios of **3-10a**/sum of the C1 & C2 isomers; [c] The corresponding nonaflate was used instead of triflate; [d] Yield refer to the isolated mixture of cross-coupling products on 1.0 mmol scale.

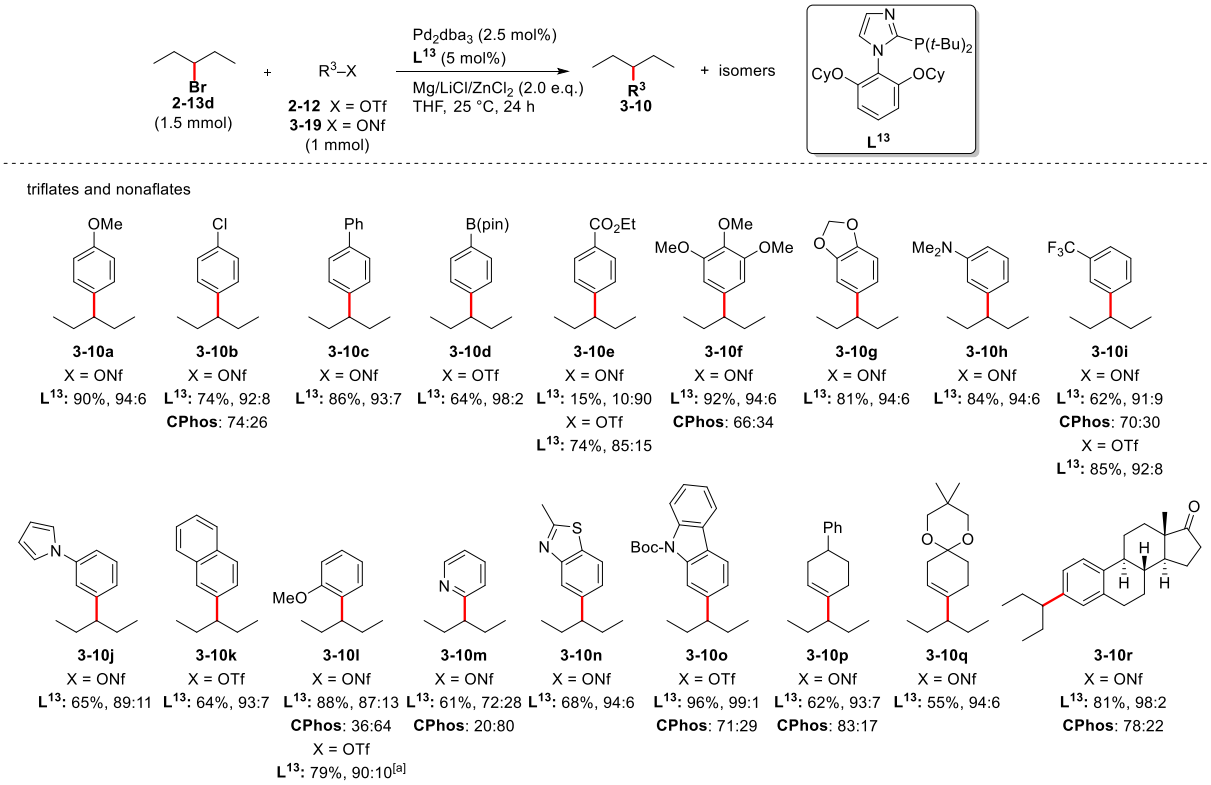
Further refinement was then conducted using the optimal ligand. Decreasing the catalyst loading from 5.0 mol% to 2.5 mol% resulted in a lower yield but the selectivity was maintained (entry 1 VS. entry 2). Comparable yield and selectivity was obtained when 1.5 equiv. organozinc species was used (entry 1 VS. entry 3). Interestingly, the reaction could be performed even at room temperature (25 °C) with similar results (entry 4). Compared to aryl triflates, the corresponding nonaflates were believed to be less expensive and more reactive.[81] Therefore, the nonaflate was utilized as the coupling partner in the reaction, affording the coupling products in 90% yield and 94% selectivity for the direct coupling product (entry 4).

2.2 Scope and limitations

2.2.1 Variation of triflates and nonaflates

Under the established reaction conditions, various triflates and nonaflates were then investigated with 3-bromopentane. In general, electron-rich and withdrawing groups at the *para*- and *meta*-positions of aryl nonaflates were well tolerated, delivering the *ipso*-products in good to excellent yields and selectivities (**3-10a** to **3-10j**). Interesting groups, such as a chloride (**3-10b**) and a boronate (**3-10d**), were also tolerated under the current reaction conditions, which could be used for further functionalization. A naphthyl ring was also a

suitable substrate (**3-10k**). Surprisingly, a nonaflate bearing an ethyl ester group gave mainly the migrative product (10:90) in quite a low yield. A control experiment with the preformed organozinc compound resulted in 85% selectivity for the direct coupling product **3-10e**. This further illustrates the huge difference between Negishi couplings performed under normal and Barbier conditions. Fortunately, the corresponding triflate provided a solution to this problem, and compound **3-10e** was obtained with a same selectivity as in the normal Negishi coupling. In general, our newly developed phosphine ligand **L**[13] showed superior selectivities compared to CPhos, especially for some challenging cases. This could be further demonstrated by the reaction with the *ortho*-substituted aryl nonaflate and triflate (**2-12l**, **3-19l**) and as well as the pyridine nonaflate (**3-19m**). Although moderate selectivities were observed for these two cases with our ligand, CPhos afforded a reversed selectivity. The other tested heteroaryl nonaflates proceeded smoothly, giving very good selectivities for the desired products (**3-10n** & **3-10o**) under the established reaction conditions. In addition, alkenyl nonaflates were also suitable in the optimal Barbier conditions, giving the products in good yields and selectivities (**3-10p** & **3-10q**). To our delight, the developed direct Barbier-Negishi couplings could be used for late-stage modification of a structurally complex compound, estrone-derived nonaflate, affording product **3-10r** in 81% yield and 98% *ipso*-selectivity. Of note, enolate formation and subsequent nucleophilic addition to the free ketone was not observed in this case, which further illustrates the excellent functional group tolerance of the developed method.



[a] With 2.0 equiv. of 3-bromopentane, Mg, LiCl and $ZnCl_2$.

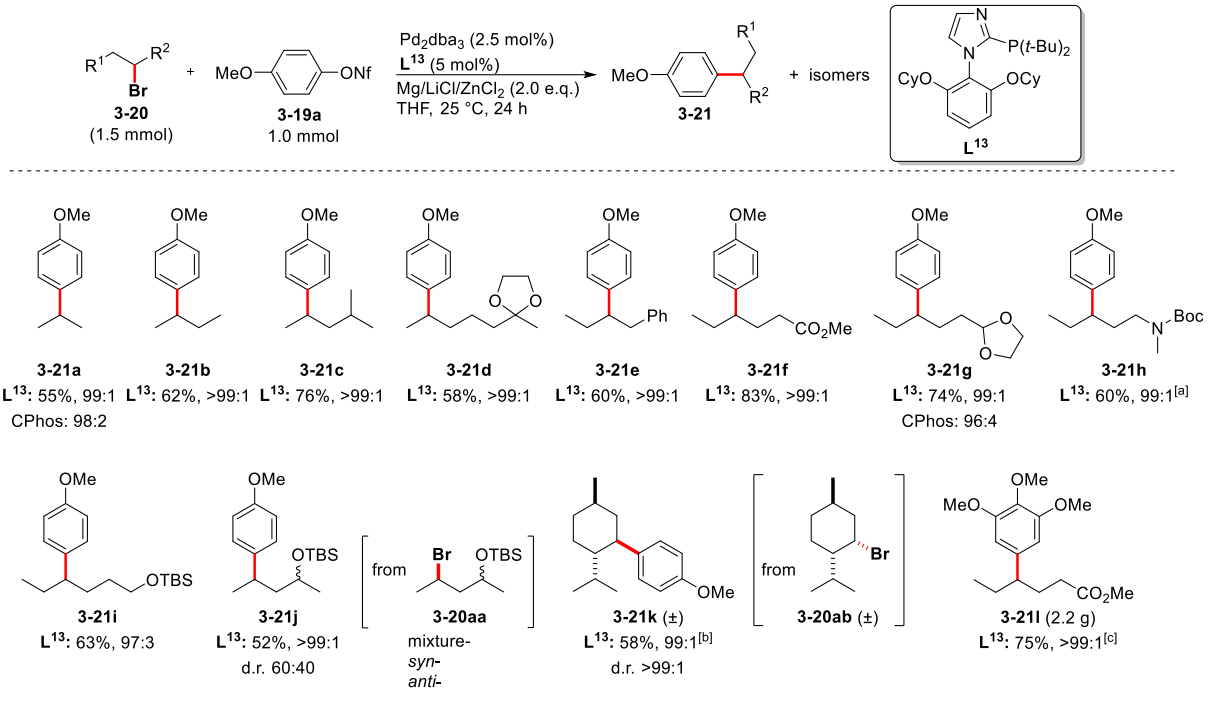
Scheme 3.8. Scope and limitations with respect to triflates and nonaflates

2.2.2 Variation of secondary alkyl bromides

Variation of secondary alkyl bromides was next studied using 4-methoxyphenyl nonaflate **3-19a** as the coupling partner. As shown in Scheme 3.9, reactions of secondary alkyl bromides with various functional groups proceeded smoothly, giving the desired direct coupling products in good yields and excellent selectivities. In this part, comparable selectivities in several cases were also observed when CPhos was used as the ligand. The superior selectivity obtained in the reaction of alkyl bromides with functional groups is still unclear so far.

Acyclic secondary bromides **3-20aa** with a 1:1 diastereomeric mixture also reacted well with 4-methoxyphenyl nonaflate **3-19a**, albeit with a low diastereoselectivity.[82] Same results were obtained with isolated pure *syn*- and *anti*- diastereomers of **3-20aa**. On the contrary, the reaction of cyclic bromide **3-20ab** furnished product **3-21k** with excellent diastereoselectivity, which is in agreement with the work of Knochel and co-workers.[83]

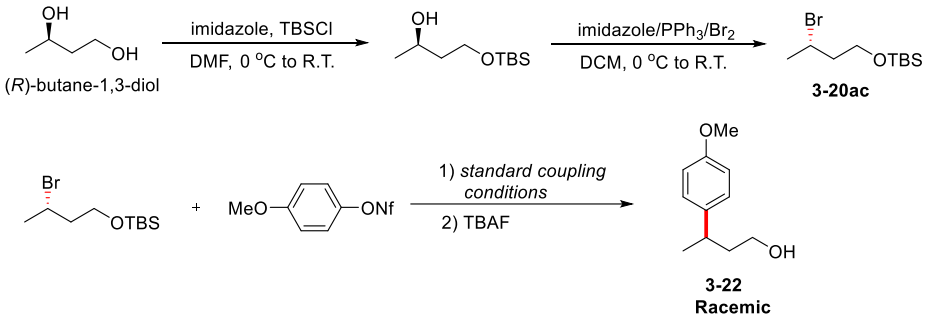
Moreover, due to the mild and easily operational reaction conditions, the reaction could be scaled-up to 10 mmol easily, giving rise to 2.2 g arylated product **3-21l** in 75% yield at a reduced catalyst loading (2.5 mol% Pd/L).



[a] With 2.0 equiv. of the bromoalkane, Mg, LiCl and $ZnCl_2$, 5.0 mol%Pd_2dba_3, and 10 mol% **L**^{13} at 60 °C; [b] With 2.0 equiv. of the bromoalkane, Mg, LiCl and $ZnCl_2$ at 40 °C; [c] With 1.25 mol%Pd_2dba_3, and 2.5 mol% **L**^{13}.

Scheme 3.9. Scope and limitations with respect to secondary alkyl bromides

Optical enriched secondary alkyl bromide **3-20ac** was prepared according to the literature[84] and subsequently engaged in the direct Barbier-Negishi coupling under the established conditions. After deprotection, **3-22** was obtained as a racemic product. Combining this result and the reaction with **3-20aa**, it is still difficult to control the stereoselectivity in this Barbier-Negishi coupling for the acyclic system. We envisaged that the radical magnesium insertion process probably induced the loss of stereoselectivity.



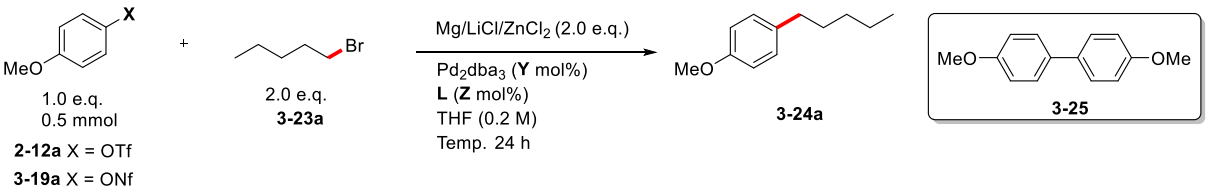
Scheme 3.10. Optical enriched alkyl bromide engaged in the direct Barbier-Negishi coupling

3. Direct Barbier-Negishi coupling of primary alkyl bromides with aryl nonaflates

3.1 Optimization of the reaction conditions

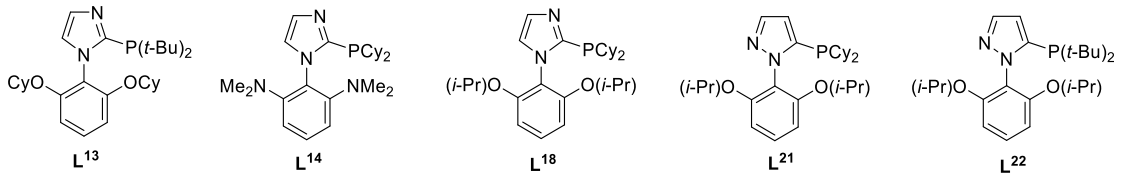
To further investigate the generality of the reaction, primary alkyl bromides were then tested in the Barbier conditions. To our surprise, only trace amount of the desired coupling product was observed from GC-MS in the reaction of 1-bromopentane with aryl triflate **2-12a**. Major homocoupling product **3-25** was observed in the reaction mixture (entry 1). Then, more attention was turned to the screening of other newly synthesized phosphine ligands (Table 3.3). Fortunately, less electron-rich pyrazole-based phosphines afforded a solution to this problem (entries 4 & 5). In particular, using $\mathbf{L^{21}}$ as the ligand gave the best result in the coupling of 1-bromopentane with 4-methoxyphenyl triflate (entry 4). Changing the leaving group from triflate to nonaflate gave the same result (entry 6). Increasing the catalyst loading to 10 mol% achieved full conversion (entry 7). Further refinement showed that the reaction could also be run at 25 °C without decreased efficiency (entry 9), giving the desired coupling product **3-24a** in 90% yield.

Table 3.3. Optimization of Barbier-Negishi coupling of triflates and nonaflates with 1-bromopentane



Entry	X	L	Y	Z	Temp. (°C)	2-12a or 3-19a/3-24a/3-25 [a]
01	OTf	$\mathbf{L^{13}}$	2.5	5.0	60	6/19/75
02	OTf	$\mathbf{L^{18}}$	2.5	5.0	60	86/14/<1
03	OTf	$\mathbf{L^{14}}$	2.5	5.0	60	84/15/<1
04	OTf	$\mathbf{L^{21}}$	2.5	5.0	60	13/84/3
05	OTf	$\mathbf{L^{22}}$	2.5	5.0	60	17/63/20
06	ONf	$\mathbf{L^{21}}$	2.5	5.0	60	12/86/2
07	ONf	$\mathbf{L^{21}}$	5.0	10.0	60	1/94/5
08	ONf	$\mathbf{L^{21}}$	5.0	10.0	40	3/93/4
09	ONf	$\mathbf{L^{21}}$	5.0	10.0	25	1/96/3 (90%)[b]

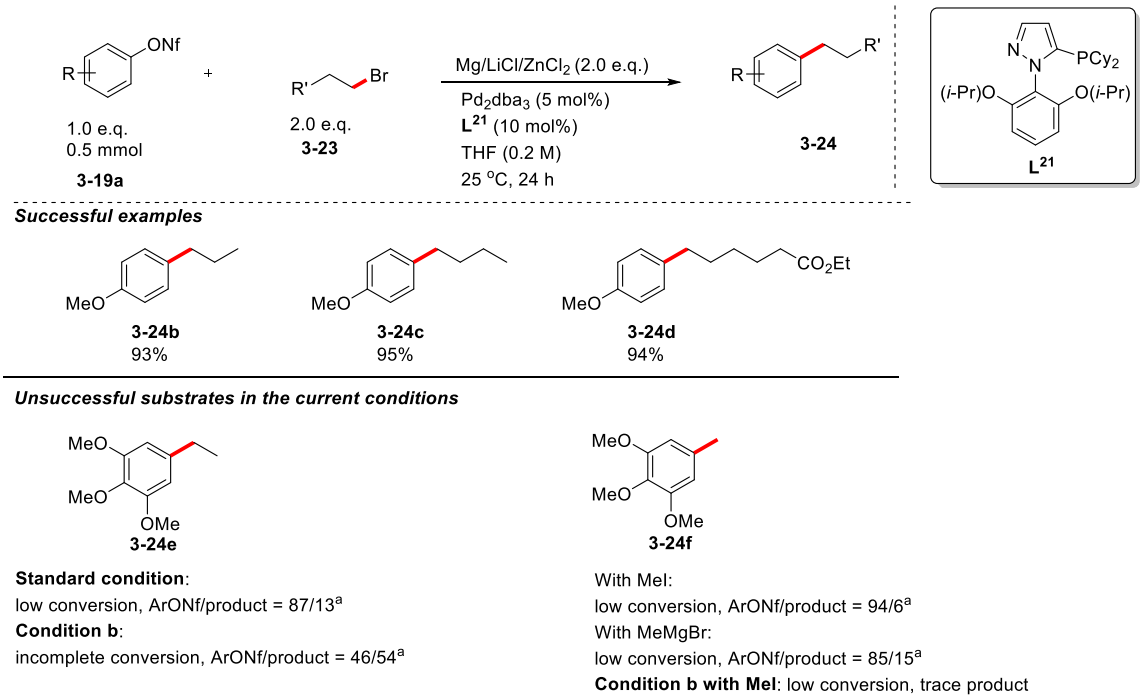
[a] The ratio was estimated by GC-MS; [b] isolated yield based on 1.0 mmol scale.



3.2 Extended examples

Under the optimal reaction conditions, other primary alkyl bromides were further examined. In general, the reactions proceeded smoothly with different primary alkyl bromides, delivering the desired coupling products in >90% yield (Scheme 3.11: **3-24b**, **3-24c**, **3-24d**).

The couplings with short-chain primary alkyl halides were challenging under the current reaction conditions, since low conversions were observed in the cases of bromoethane and methyl iodide even under harsh reaction conditions (4.0 equiv. organozinc species, high concentration of reaction mixture, high reaction temperature). For the methylation, commercially available methylmagnesium bromide solution was used directly as a control experiment, however, no significant improvement was obtained (Scheme 3.11).



[a] The ratio was estimated by GC-MS;

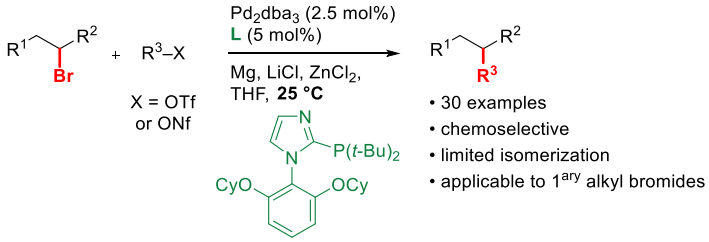
Condition b: alkyl halide/Mg/LiCl/$ZnCl_2$ (4.0 eq.), Pd_2dba_3 (5.0 mol%), **L**^{21} (10 mol%), THF (0.4 M), 60 °C, 24 h.

Scheme 3.11. Scope and limitations of Barbier-Negishi coupling with primary alkyl halides

4. Conclusion

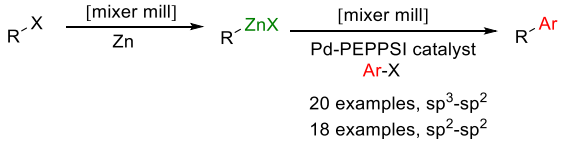
In summary, a mild and practical Barbier-Negishi cross-coupling reaction has been developed. This one-pot reaction is easily operational, avoiding handle of the moisture-sensitive organozinc compounds. Based on previous studies, a series of rigid and steric bulk, azole-based phosphine ligands were designed and applied to the coupling of secondary alkyl

bromides with triflates and nonaflates. We were pleased to find that part of the newly synthesized ligands furnished better selectivities than the reported ones. Of note, the imidazole-based phosphine with *t*-butyl substituents on the phosphorus atom and two cyclohexyloxy groups on the 2',6'-positions (highlighted in green) provided the best results, leading to the desired *ipso*-products in good yields, chemo-, and site selectivities. Meanwhile, the established Barbier conditions could be applied to the primary alkyl bromides in excellent yields by using an analogous pyrazole-based ligand.



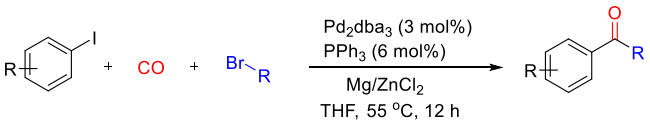
Scheme 3.12. Overview of direct Barbier-Negishi couplings of secondary alkyl bromides

During the preparation of this Ph.D. manuscript, Browne and co-workers reported mechanochemical methods to achieve the direct generation and consumption of organozinc reagents in a Negishi coupling process, allowing the formation of both C(sp^2)-C(sp^2) and C(sp^2)-C(sp^3) bonds in one-pot.[85]



Scheme 3.13. Overview of mechanochemical activation of zinc and application to Negishi cross-coupling

In addition, a palladium-catalyzed carbonylative Barbier-Negishi coupling of aryl iodide with unactivated primary and secondary alkyl bromides was developed by Wu and co-workers. The present method provides a mild procedure for the preparation of aryl alkyl ketones.[86]



Scheme 3.14. Overview of the palladium-catalyzed carbonylative Barbier-Negishi coupling

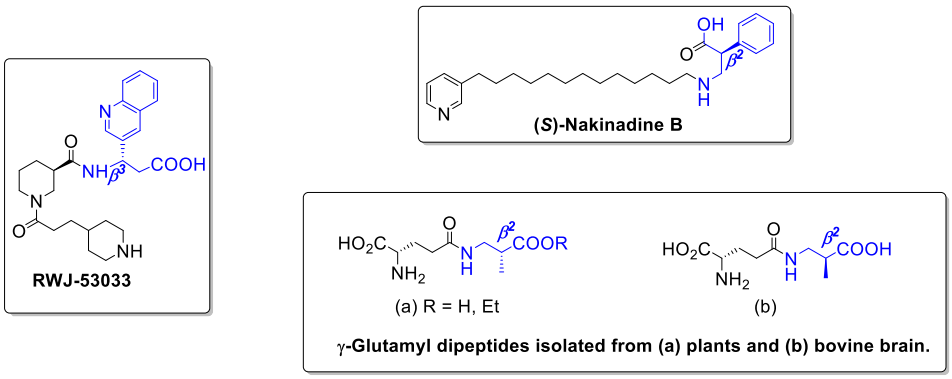
Chapter 4

Enantioselective divergent functionalization of *N*-Boc-1,3-oxazinanes: Application to the synthesis of enantioenriched β^2- and β^3-amino acids

1. Introduction and research plan

1.1 Enantiopure β^2- and β^3-amino acids: importance and preparation

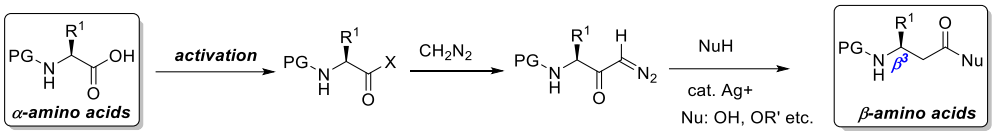
β-amino acids, especially β^2- and β^3-amino acids, not only exhibit broad biological activity but also are important and unique building blocks of natural products and peptides.[87] (*S*)-Nakinadine B has been shown to possess significant cytotoxicity against a variety of tumour cell lines including L1210 murine leukaemia and KB human epidermoid carcinoma cells.[88] Another example bearing a β^3-amino acid motif shown here is RWJ-53033, a potent nonpeptide integrin antagonist (Scheme 4.1).[89,90]



Scheme 4.1. Selected β^2-, β^3-amino acids motifs found in natural products

Due to the special properties and significance of β^2- and β^3-amino acids, it is not surprising that developing new methodologies to effeciently and enantioselectively construct these motifs has become an important and challenging endeavour for synthetic chemists.

α-amino acids are believed to be ideal starting materials for the preparation of β-amino acids. This is due to the fact that a variety of methods for their synthesis are available.[91] Another important reason is that the stereogenic center present in these compounds is retained without significant racemization in the homologated β-amino acids when suitable methods are utilized. Among all the developed methods, the Arndt-Eistert homologation sequence is superior in effectiveness (Scheme 4.2).[92] The α-amino acid is first activated and then reacted with diazomethane to form a diazoketone. After a Wolff rearrangement,[93] the desired β-amino acids can be generated efficiently. However, compared to β^3-amino acids, the β^2-anolugues cannot be prepared stereospecifically by using the same method.[87, 94]



Scheme 4.2. Arndt-Eistert homologation sequence with α-amino acids

From the retrosynthetic analysis of β^2-amino acid derivatives, different synthetic routes could be designed as outlined in Figure 4.1.[95] The Mannich reaction provides a mild and easy synthetic pathway to build the C(2)-C(3) bond (**path a**).[96] The C(2)-R bond can be formed either by α-alkylation of chiral enolates or nucleophilic addition and substitution (**path b**).[97] β^2-amino acid derivatives can also be synthesized by asymmetric hydrogenation (**path c**)[98] and asymmetric conjugate addition is usually utilized to construct the C(2)-C(1) bond (**path d**)[99].

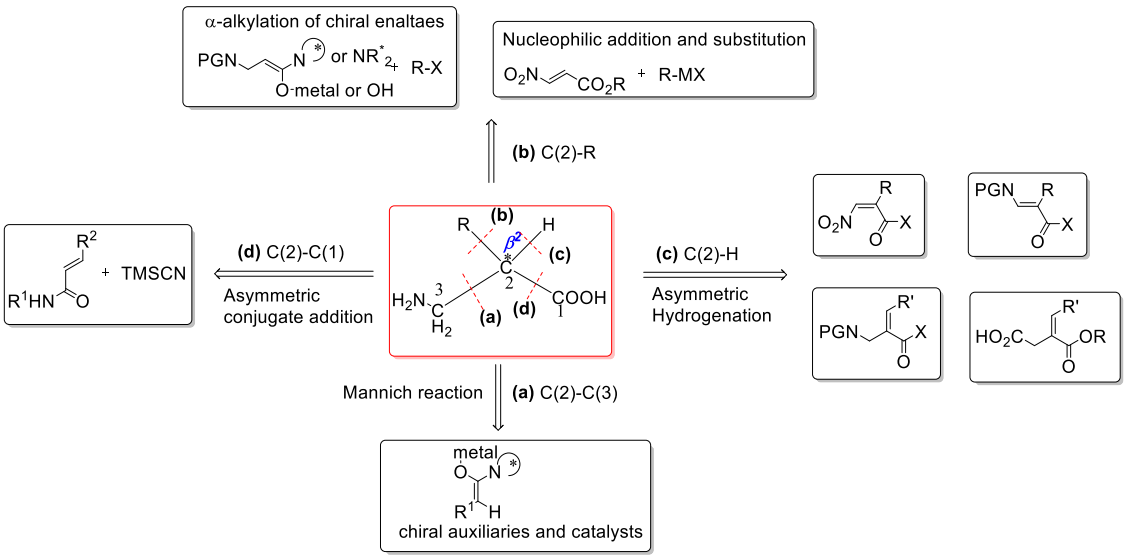
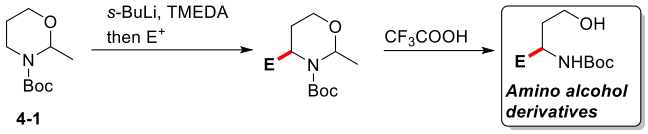


Figure 4.1. Overview of disconnections to synthesize β^2-amino acids

Although various methodologies have been developed for the preparation of β^2- or β^3-amino acids, a general method to efficiently synthesize both enantiopure β^2- and β^3-amino acids needs to be developed.

1.2 Chemistry of *N*-Boc-1,3-oxazinanes

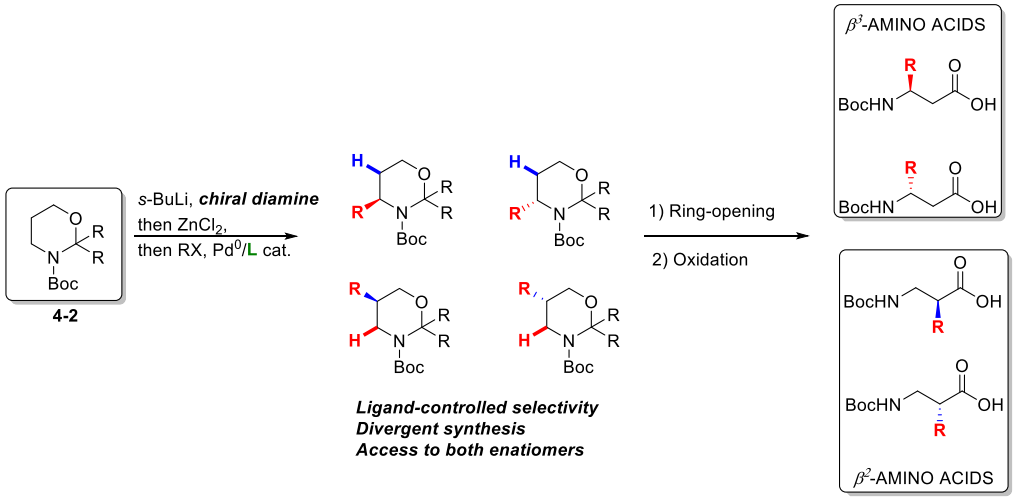
N-Boc-1,3-oxazinanes were firstly studied by Beak and co-workers, as α-metalo amine synthetic equivalents of unactivated primary amines.[100] Upon trapping of the organolithium intermediate with a variety of electrophiles followed by hydrolysis, useful amino alcohols and amino acid derivatives could be obtained.



Scheme 4.3. Lithiation chemistry of *N*-Boc-tetrahydro-1,3-oxazine

1.3 Research plan

Since *N*-Boc-1,3-oxazinanes can be regarded as synthetic equivalent of amino alcohol derivatives, in this part, we would like to take advantage of these substrates to achieve the enantiodivergent synthesis of a series of both β^2- and β^3-amino acids. Based on our previous studies, we envisaged that both α- and β-functionalized products could be generated by using the ‘‘ligand-controlled selectivity’’ strategy.[24] Moreover, depending on the configuration of the used chiral diamines, both enantiomers could be accessed. After ring-opening and further oxidation, divergent β-amino acid derivatives could be reached.



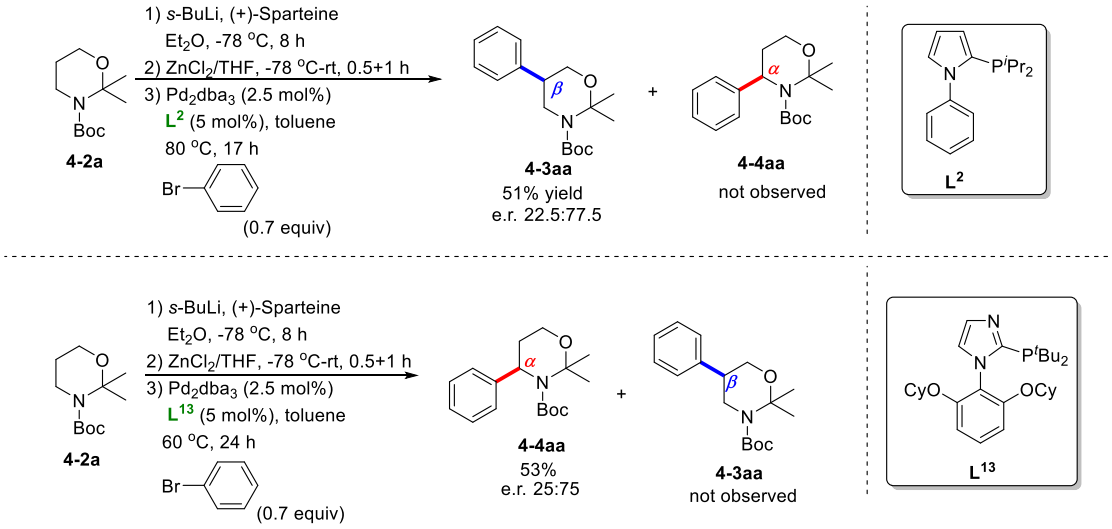
Scheme 4.4. Overview of research plan

2. Research part

2.1 Initial study

Together with Dr. Weilong Lin, we firstly studied on the arylation of the organozinc species, generated *in-situ* by a sequence of α-lithiation of *N*-Boc-1,3-oxazinane **4-2a** and transmetalation with $ZnCl_2$, with phenyl bromide (Scheme 4.5). By using the same catalytic system as for the β-arylation of *N*-Boc piperidines developed by our group in 2013,[51] we were delighted to find that the β-arylated product was obtained as the only isomer. In addition, an inspiring enantioselectivity (77.5:22.5) was observed when (+)-sparteine was engaged in the

lithiation step. Switching of the ligand to the bulky phosphine ligand **L^{13}**,[101] a completely reversed selectivity was obtained as expected. With these promising results in hand, we next further investigated both α- and β-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes and applied this methodology to the synthesis of β-amino acids.



Scheme 4.5. Initial results obtained by Dr. Weilong Lin

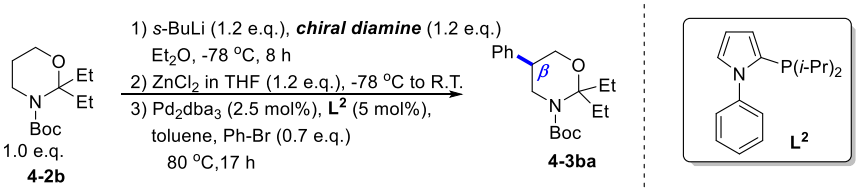
2.2 Enantioselective β-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes

2.2.1 Effect of chiral diamines

Later, we discovered that when two ethyl groups were installed instead of the methyl groups, the enantioselectivity was greatly improved to 3:97 even though the yield remained moderate in the presence of (+)-sparteine (Table 4.1, entry 1). Therefore, the reaction conditions were further optimized using substrate **4-2b**.

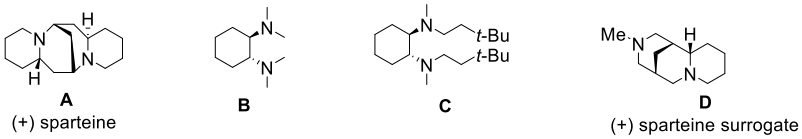
First of all, the effect of different chiral diamines was examined. Although (+)-sparteine gave a low reactivity, the other types of chiral diamines furnished the expected β-arylated product in good yields with different e.r. (entry 2-5). Noteworthy, the (+)-sparteine surrogate developed by the group of O'Brien[102] affored the β-product with 81% yield and 6:94 e.r. (entry 5). Due to its high reactivity, the (+)-sparteine surrogate, has to be stored in the freezer of the glovebox after distillation or distilled prior to use (entry 4 VS. entry 5). Since (+)-sparteine gave a higher enantioselectivity but a lower yield, whereas the (+)-sparteine surrogate was highly reactive but induced a lower enantioselectivity, at this stage, two different strategies can be proposed: improving e.r. using the (+)-sparteine surrogate or trying to increase the yield in the presence of (+)-sparteine.

Table 4.1. Effect of chiral diamines



Entry	Chiral diamine	Yield[a]	e.r.[b]
1	**A**	48%	3:97
2	**B**	70%	48:52
3	**C**	76%	91:9
4[c]	**D**	78%	8:92
5[d]	**D**	81%	6:94

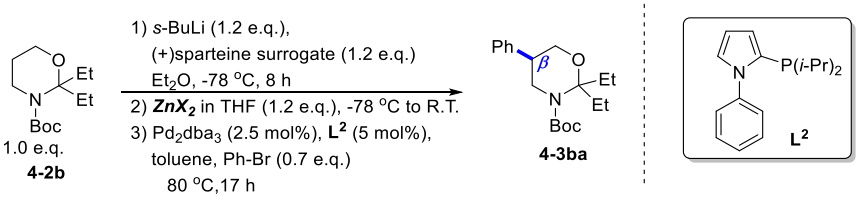
[a] Isolated yield; [b] Determined by chiral HPLC; [c] (+) sparteine surrogate was distillated and stored in the freezer outside of the glovebox; [d] (+) sparteine surrogate was distillated and stored in the freezer of the glovebox.



2.2.2 Effect of zinc sources

Previous studies showed that zinc source has an important impact on the enantioselectivity. Therefore, representative zinc salts were tested in combination of the (+)-sparteine surrogate. Good yields were obtained in all cases. Nevertheless, comparable enantioselectivities were observed in these cases (entries 1-4). Among all the zinc salts examined, zinc chloride gave the best results (entry 1).

Table 4.2. Effect of zinc sources

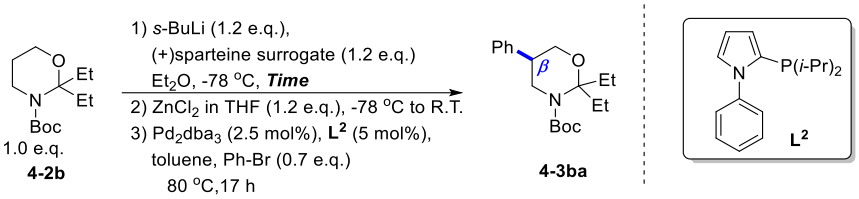


Entry	ZnX_2	Yield (%)[a]	e.r.[b]
1	$ZnCl_2$	81	6:94
2	$Zn(OAc)_2$	83	9:91
3	$ZnBr_2$	73	8:92
4	$Zn(OPiv)_2$	81	9:91

[a] Isolated yield; [b] Determined by chiral HPLC.

2.2.3 Effect of asymmetric lithiation time

Table 4.3. Effect of asymmetric lithiation time with (+)-sparteine surrogate



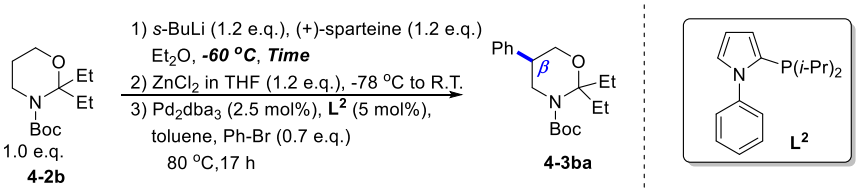
Entry	Time	Yield (%)[a]	e.r.[b]
1	8.0 h	89	6:94
2	5.0 h	80	6:94
3	3.0 h	77	6:94
4	1.0 h	54	5.5:94.5

[a] The yield was determined by crude ^{1}H-NMR using dibromomethane as the internal standard; [b] Determined by chiral HPLC.

The lithiation time was next studied when (+)-sparteine surrogate was engaged in the lithiation step. Previous studies in our group showed that the racemization could occur if the lithiation was performed for too long. Since (+)-sparteine surrogate is reported to be more reactive than the other chiral diamines,[103] we envisaged that we could reduce the lithiation time, expecting to achieve a higher enantioselectivity. The lithiation step was performed in 8.0 h, 5.0 h, 3.0 h and 1.0 h respectively and the results are shown in Table 4.3. Decreasing the lithiation time resulted in a lower yield while the enantioselectivity was maintained.

On the other hand, the effect of asymmetric lithiation time was also examined when (+)-sparteine was used at -60 °C.[104] But unfortunately no better results were achieved (Table 4.4). Meantime, increasing the lithiation temperature from -78 °C to -60 °C only gave a decreased e.r..

Table 4.4. Effect of asymmetric lithiation time with (+)-sparteine



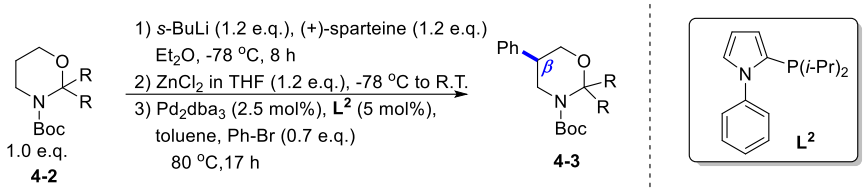
Entry	Time	Yield[a]	e.r.[b]
1	8.0 h	52%	5:95
2	5.0 h	51%	5:95

[a] Isolated yield; [b] Determined by chiral HPLC.

2.2.4 Effect of R group

Although various reaction parameters were investigated, we could not achieve this reaction with good yield and excellent enantioselectivity. Due to the fact that substrate **4-2b** with two ethyl groups gave better results than substrate **4-2a** with two methyl groups, we next turned our attention to study the effect of different R groups.

Table 4.5. Effect of R group

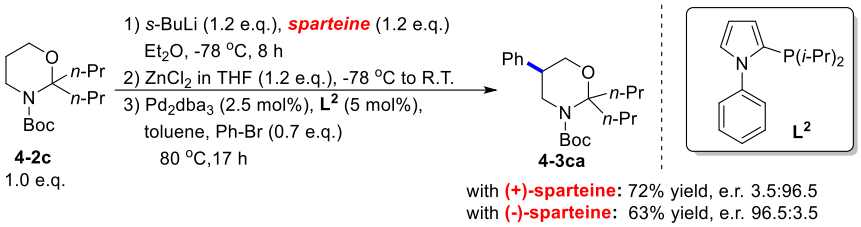


Entry	R	Yield (%)[a]	e.r.[b]
1	Me (**4-2a**)	51	22.5:77.5
2	Et (**4-2b**)	48	3:97
3	*n*-Pr (**4-2c**)	72	3.5:96.5
4	Cyclohexyl (**4-2d**)	8	11:89
5	Cyclopentyl (**4-2e**)	23	15:85
6[c]	*n*-Pr (**4-2c**)	63	96.5:3.5
7[d]	*n*-Pr (**4-2c**)	72	3:97
8[d]	Et (**4-2b**)	49	3.5:96.5

[a] Isolated yield; [b] Determined by chiral HPLC; [c] (-)-sparteine was used; [d] 4-bromoanisole was tested instead.

As it can be seen from Table 4.5, the *gem*-substituents were found to have a pronounced impact on the yield, as well as the enantioselectivity. While two methyl groups gave a moderate yield and enantioselectivity (entry 1), a remarkably enhanced enantioselectivity was obtained when two ethyl and *n*-propyl groups were installed in the *N*-Boc-1,3-oxazinanes (entries 2-3), with the two *n*-propyl groups as the optimal substrate (entry 3). This could be further demonstrated when 4-bromoanisole was used as the coupling partner (entries 7-8). On the contrary, the reactivities with cyclic substituents, such as cyclohexyl and cyclopentyl groups, developed by Dr. Weilong Lin, were found to be quite low, although the enantioselectivities were improved compared to the two methyl groups (entries 4-5 VS. entry 1). As expected, (-)-sparteine gave the opposite enantiomer with similar results (entry 6).

2.2.5 Optimal reaction conditions



Scheme 4.6. Optimal reaction conditions

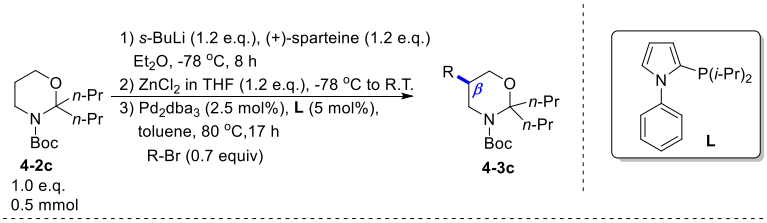
2.2.6 Scope and limitations

Under the established reaction conditions, the scope and limitations of the enantioslective *β*-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes were next evaluated.

In general, good yields and high enantioselectivities were obtained regardless of the electron properties and substituents positions of aryl bromides. The developed reaction conditions were found to tolerate a range of mono- and di-substituted bromobenzenes. Moreover, 2-bromonaphthalene was successfully engaged in the reaction, giving rise to the corresponding product in 60% yield with 4.5:95.5 e.r. (**4-3co**). (-)-sparteine was also tested under the current reaction conditions, showing that both enantiomers could be easily generated.

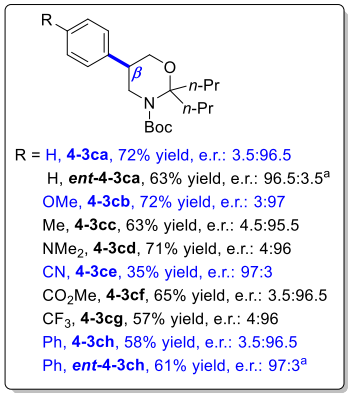
Interestingly, when the heteroaryl bromides are electron-withdrawing, a mixture of two isomers was observed (desired *β*/new isomer 80:20, observed from GC-MS). According to a preliminary inspection of ^{1}H-NMR of the isolated mixture, we suspected that the other isomer observed could be the *γ*-arylated product. However, due to the similar R_f, it was not possible to isolated the pure *γ*-product. Further efforts will be conducted in order to confirm the structure of the new isomer.

To show the generality of our developed reaction, the use of alkenyl bromides and alkenyl triflate was also investigated. Pleasingly, the desired *β*-products were obtained with satisfying results.

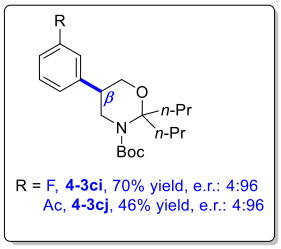


Examples of aryl bromides

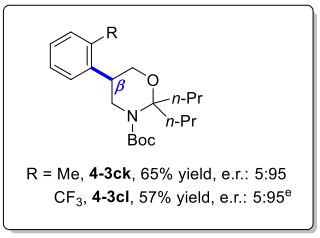
p-substituted:



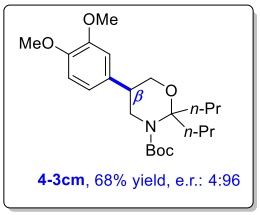
m-substituted:

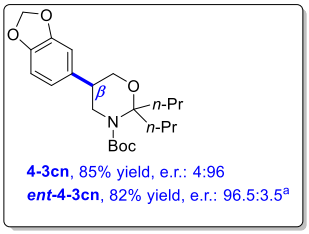


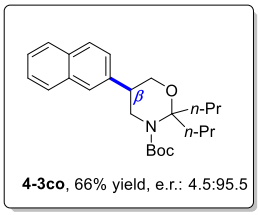
o-substituted:



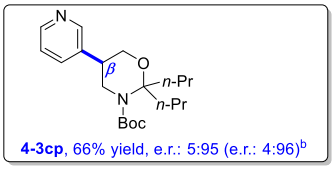
others:

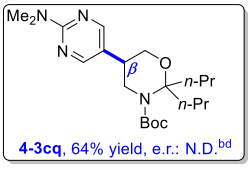


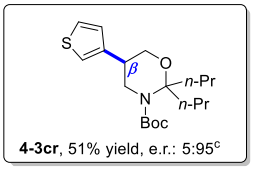




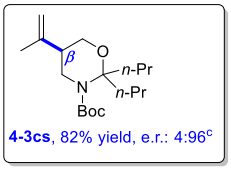
Examples of heteroaryl bromides

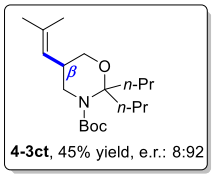


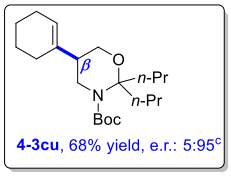


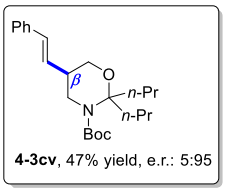


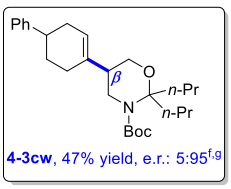
Examples of Alkenyl bromides/triflate











[a] With (-)-sparteine; [b] Yield refers to the yield of mixture of *β*- and *γ*-products (GC-MS ratio: around 80:20), and the value in parenthesis is e.r. of *γ*-product; [c] The e.r. was determined by ring-opening to form the corresponding amino alcohols; [d] No good conditions found for the

separation on chiral HPLC; [e] DavePhos was used; [f] The e.r. has to be checked, since one peak is partially overlapped with another minor peak on chiral HPLC; [g] ROTf was used.
Reactions performed by myself are highlighted in blue.

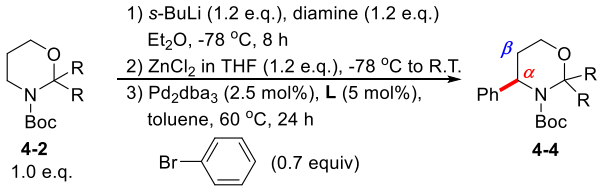
Scheme 4.7. Scope and limitations of enantioselective *β*-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes

2.3 Enantioselective *α*-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes

2.3.1 Optimization of the reaction conditions

Enantioselective *α*-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes was also studied based on the ‘‘ligand-controlled selectivity’’ strategy.[24] According to our previous studies, representative bulky phosphine ligands were examined. Among all the tested bulky ligands, our newly designed bulky phosphine ligand **L^{13}** was again found to give the best results (entries 1-3 and entries 5-9).[101] When (+)-sparteine was used as the chiral source, a high enantioselectivity (5:95) was obtained (entry 5). In this case, the more reactive (+)-sparteine surrogate gave a similar yield but a lower enantioselectivity (entry 11). In addition, we found that shorter alkyl chains on the substrate afforded the *α*-arylated product in a higher yield, with the diethyl group as the optimal one (entry 5 VS. entry 10). Zinc source were found to have an effect on the enantioselectivty, since slightly higher enantioselectivities were obtained when $Zn(OAc)_2$ and $Zn(OPiv)_2$ were used (entries 12-13). Further optimization showed that the use of the corresponding nonaflate or triflate resulted in a higher yield at 80 °C (entries 14-16). Since $Zn(OAc)_2$ is commercially available, it will be used for the scope study.

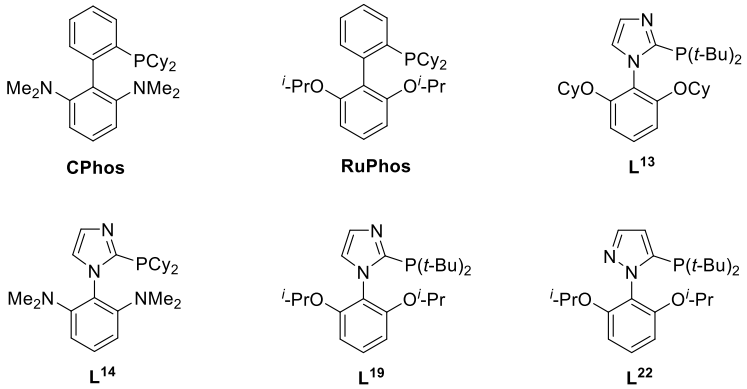
Table 4.6. Optimization of enantioselective *α*-C(sp^3)-H arylation



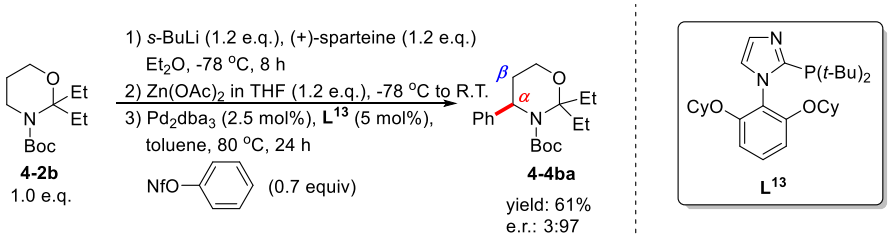
Entry	R	diamine	**L**	*α*/*β*[a]	Yield of **4-4** (%)[b]	e.r. of **4-4**[c]
1	Me	TMEDA	P*t*Bu$_3$·HBF$_4$	27/73	26	-
2	Me	TMEDA	CPhos	>98/2	20	-
3	Me	TMEDA	**L^{13}**	>98/2	54	-
4	Me	(+)-sparteine	**L^{13}**	>98/2	53	25 :75
5	Et	(+)-sparteine	**L^{13}**	>98/2	51	5:95
6	Et	(+)-sparteine	RuPhos	34/66	20	N.D.
7	Et	(+)-sparteine	**L^{14}**	88/12	43	N.D.

8	Et	(+)-sparteine	**L^{19}**	>98/2	45	N.D.
9	Et	(+)-sparteine	**L^{22}**	>98/2	38	N.D.
10	*n*-Pr	(+)-sparteine	**L^{13}**	>98/2	30	6:94
11	Et	(+)-sparteine surrogate	**L^{13}**	>98/2	46	8:91
12[d,h]	Et	(+)-sparteine	**L^{13}**	>98/2	48	3:97
13[e,h]	Et	(+)-sparteine	**L^{13}**	>98/2	51	3:97
14[f,h]	Et	(+)-sparteine	**L^{13}**	>98/2	58	3:97
15[d,g,h]	Et	(+)-sparteine	**L^{13}**	>98/2	61	3:97
16[e,g,h]	Et	(-)-sparteine	**L^{13}**	>98/2	56	3:97

[a] The ratio of α/β is determined by GC-MS or ^{1}H-NMR of the crude mixture; [b] Isolated yield; [c] Determined by chiral HPLC; [d] $Zn(OAc)_2$ was used instead of $ZnCl_2$; [e] $Zn(OPiv)_2$ was used instead of $ZnCl_2$; [f] PhOTf was used; [g] PhONf was used; [h] 80 ºC.



2.3.2 Optimal reaction conditions



Scheme 4.8. Optimal reaction conditions

2.4 Catalytic asymmetric deprotonation using a ligand exchange approach

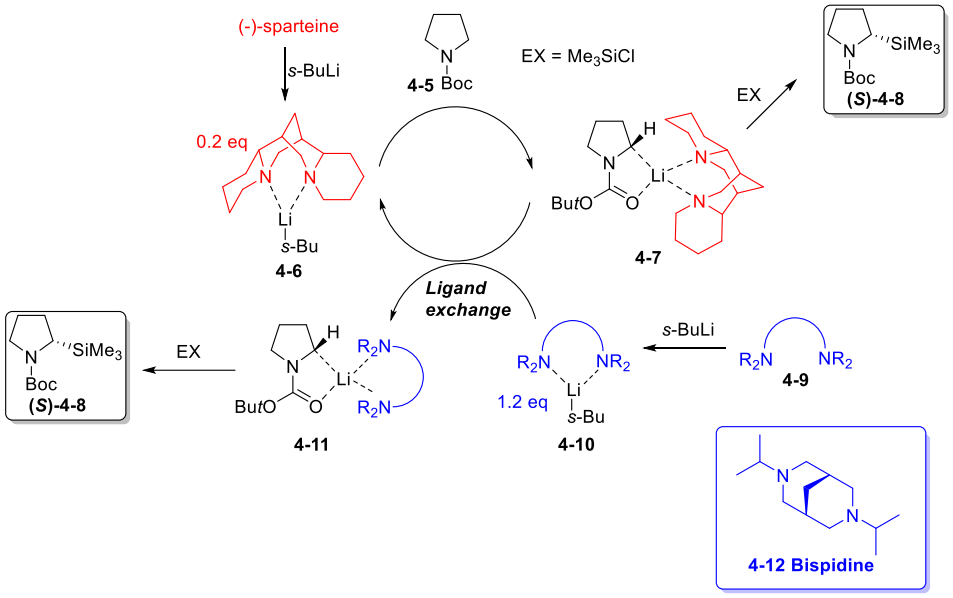
2.4.1 Proposed concept

Enantiopure sparteine is a widely utilized chiral diamine in asymmetric synthesis. In most cases, stoichiometric amount of sparteine has to be used to achieve high yields and enantioselectivities. However, reports of catalytic applications are rare. In 2005, O'Brien and co-workers made a significant breakthrough in this field. They proposed a conceptually

different catalytic approach to achieve that goal.[105] Their ligand exchange approach is outlined in Scheme 4.9 for *N*-Boc pyrrolidine **4-5**. They proposed that stoichiometric achiral diamine **4-9** would replace catalytic amount of (-)-sparteine from **4-7**, generating a new organolithium/diamine complex **4-11** and at the same time regenerating the active *s*-BuLi/(-)-sparteine complex **4-6**, which could then enter the next catalytic cycle. Complex **4-11** would then trap Me_3SiCl to afford the product **(*S*)-4-8**.

To achieve that goal, a suitable achiral diamine **4-9** needs to be well designed. In principle, several criteria must be met regarding the achiral diamine: (1) ligand exchange must occur; (2) organolithium/diamine complex **4-7** and **4-11** must be configurationally stable during the ligand exchange step; (3) deprotonation of **4-5** using *s*-BuLi/diamine complex **4-10** must be slower than that using *s*-BuLi/(-)-sparteine complex **4-6**.

After evaluating different stoichiometric achiral ligands, bispidine **4-12** gave the best results in terms of both yield and enantioselectivity.[106] With this method, each enantiomer of useful products was accessed in the presence of catalytic (-)-sparteine or (+)-sparteine surrogate.[105, 107] Moreover, later research showed that this catalytic protocol was also compatible with Negishi coupling conditions.[108]



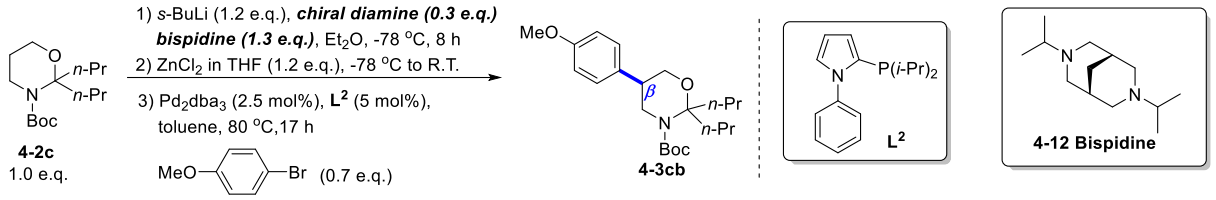
Scheme 4.9. Proposed ligand exchange strategy for the catalytic asymmetric deprotonation of *N*-Boc pyrrolidine

2.4.2 Proof-of-concept

Based on O'Brien's elegant work, we then followed a similar protocol using our system. *s*-BuLi/bispidine was used with three catalytic chiral diamines (0.3 equiv.): (+)-sparteine,

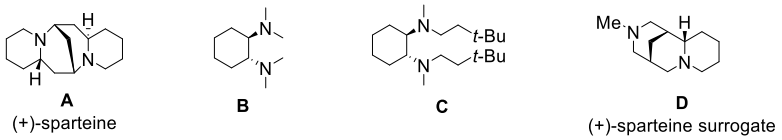
(+)-sparteine surrogate and as well as chiral diamine **C**, all of which had achieved good results in the asymmetric deprotonation of *N*-Boc-1,3-oxazinanes. Although catalytic (+)-sparteine gave the highest e.r., a disappointing yield was obtained probably due to its low reactivity (entry 1). Changing of the *gem*-substituents for less bulky ethyl groups resulted in almost the same yield and enantioselectivity (entry 2). Chiral diamine **C**, which was found to be reactive in the stoichiometric deprotonation, gave a slightly improved yield (entry 3). To our delight, the most reactive (+)-sparteine surrogate worked well in the catalytic asymmetric deprotonation, furnishing the coupling product **4-3cb** in 68% yield and 7:93 e.r. (entry 4). These results clearly demonstrated that the catalytic asymmetric lithiation using the ligand exchange approach is feasible in our system.

Table 4.7. Preliminary results on catalytic asymmetric deprotonation



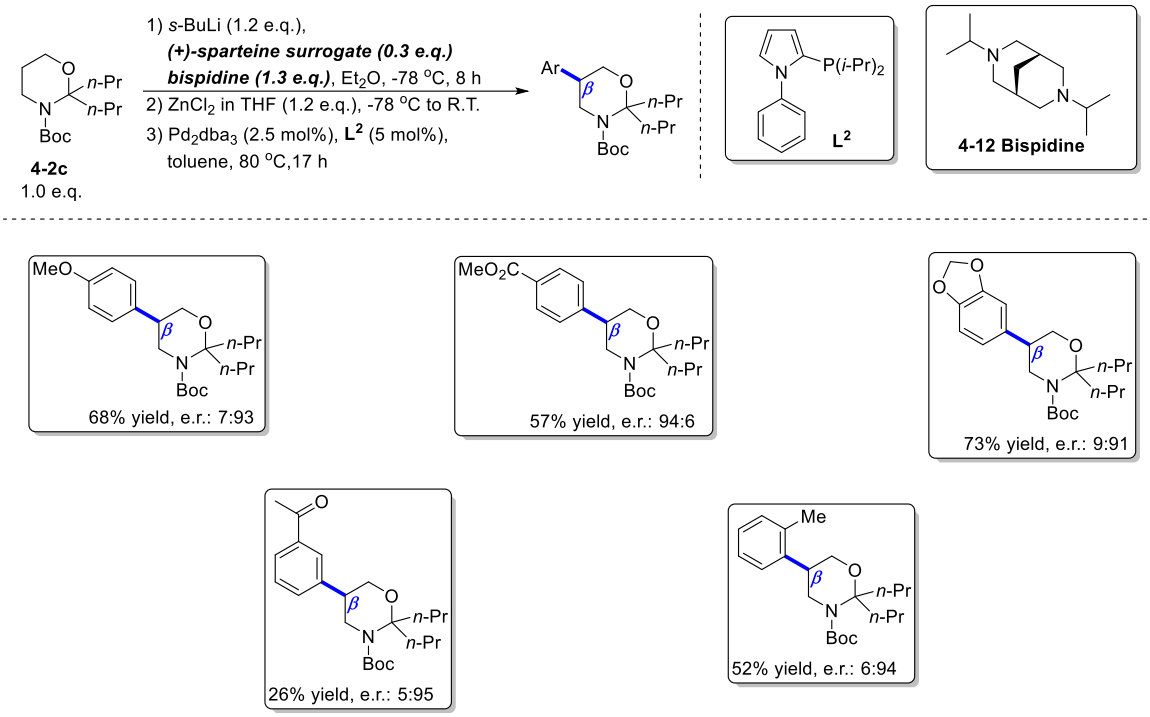
Entry	Chiral diamine	Yield (%)[a]	e.r.[b]
1	**A**	18	5:95
2[c]	**A**	12	5:95
3	**C**	38	94:6
4	**D**	68%	7:93

[a] Isolated yield; [b] Determined by chiral HPLC; [c] substrate **4.2b** with two ethyl groups was used.



2.4.3 Extended examples

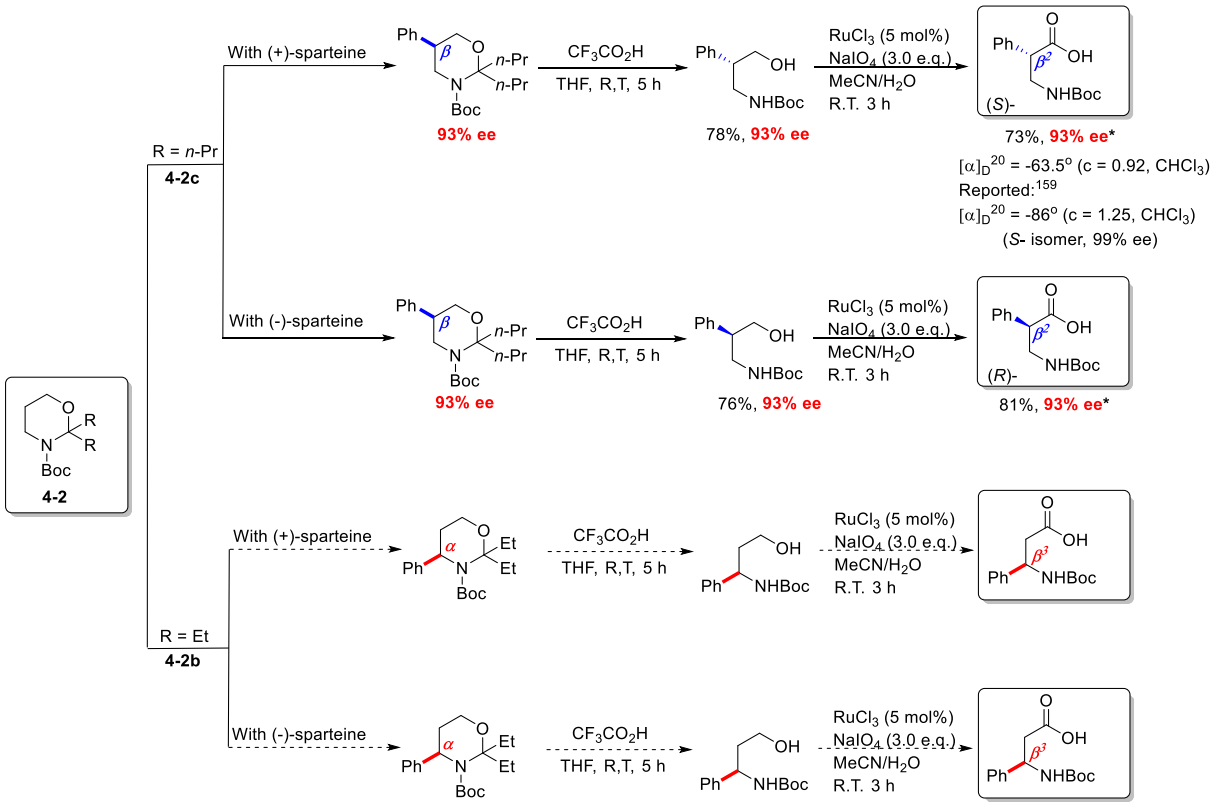
This catalytic asymmetric deprotonation was then further examined with different coupling partners. In general, good yields and more than 90:10 e.r. were obtained with electron-rich and electron-withdrawing substituents at the *ortho*-, *meta*- and *para*-positions. A low yield was obtained when 3-Ac phenyl bromide was used as the coupling partner.



Scheme 4.10. Representative examples of catalytic asymmetric deprotonation

2.5 Application to the synthesis of enantiopure β^2- and β^3-amino acids

Finally, to showcase our developed methodology, we applied it to the synthesis of enantioenriched β-amino acid derivatives. After a simple two-steps sequence of ring-opening/oxidation, the desired enantioriched β^2-amino acids could be afforded efficiently.[109] Moreover, we were pleased to find that the enantiomeric ratio was not eroded at all during these two steps. The configuration of the obtained β^2-amino acid was determined by comparing the reported specific optical rotations ($[\alpha]_D^{20}$). Similarly, we could envisage that the enantiopure β^3-amino acids could also be prepared using the same sequence. Further examination on this part is ongoing. In a word, our methodology provides a general route to the enantiodivergent synthesis of β^2- and β^3-amino acids (Scheme 4.11).

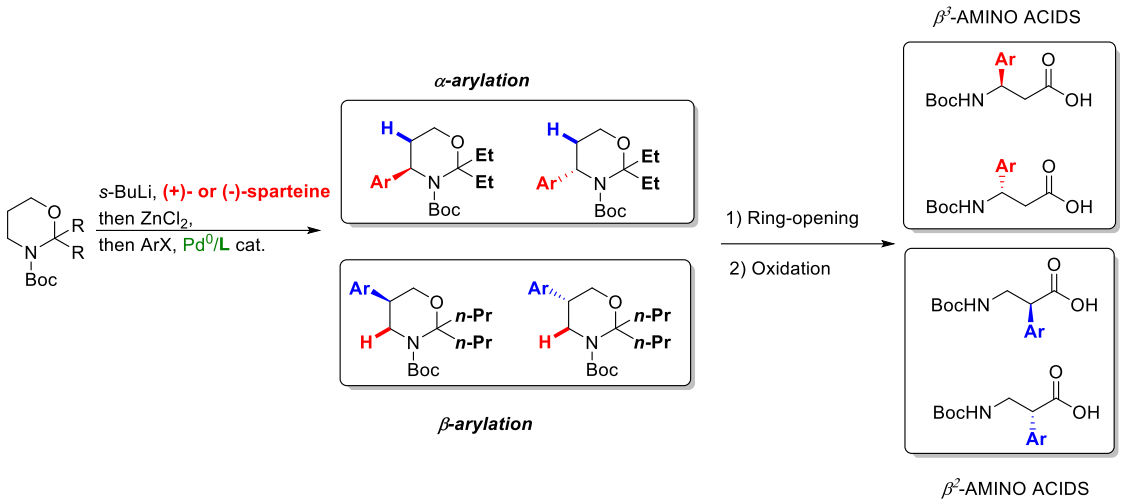


* Ee of the final amino acid derivatives were determined by the corresponding methylation product.

Scheme 4.11. Preliminary study on the application

3. Conclusion and outlook

To conclude, a versatile and highly enantiodivergent functionalization of *N*-Boc-1,3-oxazinanes was developed by combining the asymmetric deprotonation chemistry and our developed ‘‘ligand-controlled selectivity’’ strategy. The power of this methodology was preliminarily demonstrated by the efficient and divergent synthesis of enantioriched β^2- and β^3-amino acids. Moreover, preliminary study showed the feasibility of a catalytic version of the asymmetric lithiation step. Future work includes the further study of enantioselective α-C(sp^3)-H functionalization of *N*-Boc-1,3-oxazinanes and the application to the synthesis of enantiopure β^2- and β^3-amino acids. Mechanistic studies will be conducted to have a deeper understanding of the stereochemical issues during the sequence of asymmetric deprotonation/transmetalation/Negishi cross-coupling.



Scheme 4.12. Overview of enantiodivergent functionalization of *N*-Boc-1,3-oxazinanes

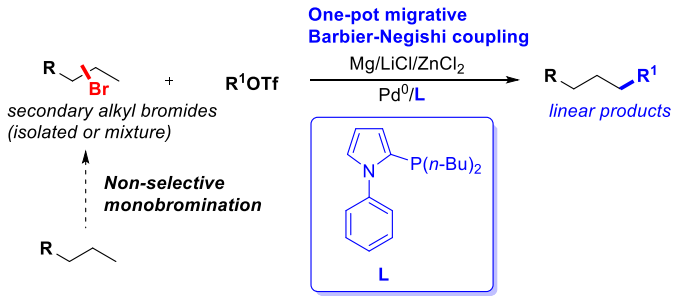
General conclusion

Over the past decades, transition metal-catalyzed cross-coupling reactions have emerged as a powerful method to construct carbon-carbon bonds, and even carbon-heterocarbon bonds. Therefore, numerous research and applications have been devoted in this field and the research on cross-coupling reactions continue to be the hot topic in both academic and industrial communities.

Although great process has been achieved in palladium-catalyzed $C(sp^2)$-$C(sp^3)$ cross-couplings, limitations and challenges still exist. Since most of the organometallics are air or/and moisture sensitive, the pre-formation of these reagents prior to the cross-couplings is normally required. Another challenging issue arises from the competitive β-hydride elimination relative to the direct reductive elimination.

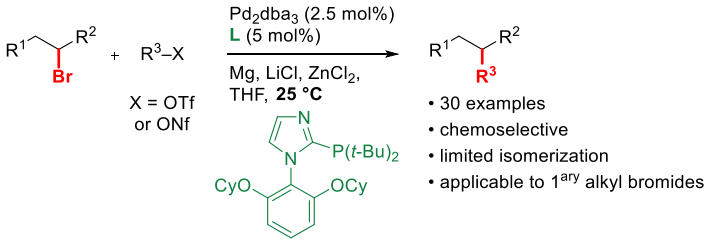
In this Ph.D thesis, we aimed to solve the two limitations in palladium-catalyzed cross-coupling reactions, trying to find and develop suitable ligands to control the site-selectivity when secondary alkylzinc reagents were used as the nucleophiles.

In the first part, based on our previous studies on migrative cross-coupling reactions, we extended the scope to the secondary alkyl bromides under easily operational Barbier conditions, where the organozincs were generated *in-situ* by magnesium insertion and transmetallation with $ZnCl_2$, and then do the cross-coupling in one-pot. Thanks to the utility of a suitable flexible phosphine ligand, a broad range of linear arylated products could be afforded with good to excellent selectivity in a regioconvergent manner. In addition, the developed strategy could be even coupled to a non-selective monobromination process, thus allowing the functionalization of simple alkanes in just two-steps.

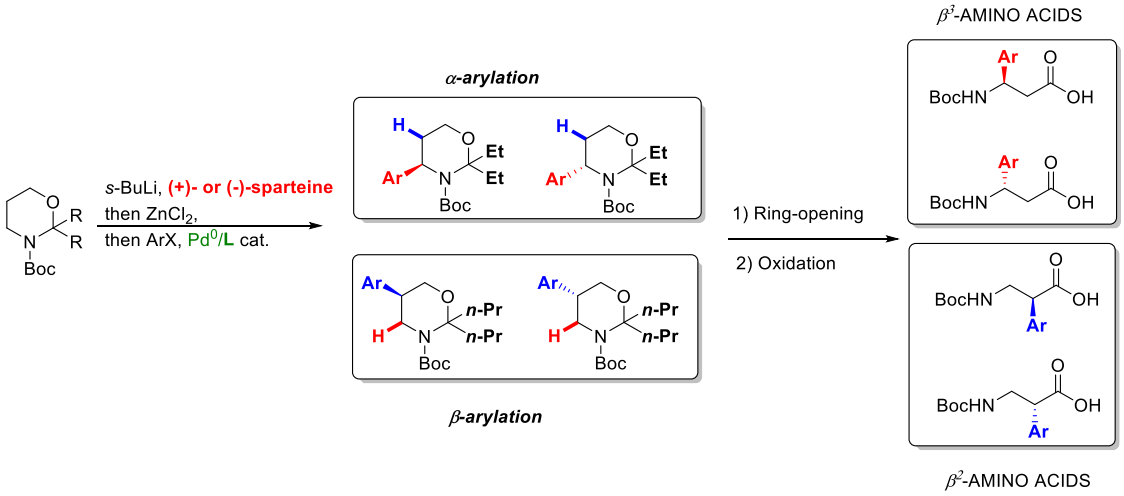


Due to the interests and challenges in the direct cross-couplings of alkyl nucleophiles containing β-hydogen(s), we continued the study on direct Barbier-Negishi cross-coupling of

secondary alkylzincs. Given the fact that reported or commercially available ligands did not achieve satisfying results, we designed and synthesized a series of azole-based bulky phosphine ligands. Under the mild conditions, good to excellent selectivities for direct cross-coupling products were obtained in the presence of palladium catalysis featuring one of our newly developed ligands (labelled green as shown below). Additionally, the Barbier conditions could be applied to the primary alkyl bromides.



In the last part of this thesis, the ‘‘ligand-controlled selectivity’’ strategy was applied to the enantiodivergent functionalization of *N*-Boc-1,3-oxazinanes. This powerful and useful methodology provided a general approach to the access of enantiopure β^2- and β^3 -amino acid derivatives. Moreover, both enantiomers of amino acids could be obtained depending on the configuration of the chiral diamines engaged in the deprotonation system. Preliminary studies showed that the asymmetric catalytic deprotonation is feasible by using the reported ligand exchange approach. Further investigation on this part is still on going.



Experimental section

1. General information

Techniques:

All reactions involving air-sensitive material were carried out in a pre-dried glassware under an argon atmosphere by using Schlenk techniques employing double-line argon-vacuum lines and working in an argon-filled glove box. Analytical thin layer chromatography (TLC) was performed using pre-coated Merck silica gel 60 F254 plates (0.25 mm). Visualization of the developed chromatogram was performed by UV absorbance (254 nm) or TLC stains ($KMnO_4$ and Phosphomolybdic acid). Flash chromatography was performed using Silicycle SiliaFlash P60 (230-400 mesh) with the indicated solvent system, using gradients of increasing polarity in most cases.

Chemicals:

Anhydrous solvents were obtained by distillation over calcium hydride or by distillation over sodium. Tetrahydrofuran (THF) and toluene were purchased from VWR (HiPerSolv CHROMANORM®, HPLC grade). Dichloromethane (for HPLC, unstabilized) was purchased from Fischer Chemical. Et_2O (Spectrophotometric Grade, 99+%, inhibitor free) was purchased from Alfa Aesar. The solvents were predried unter nitrogen over activated molecular sieve for a week. Then they were transferred under nitrogen into the storrage kegs of a PureSolve MD5 solvent purification system from inert®. In this system the solvents were then purified by passing them under nitrogen pressure through two packed columns of acitvated basic alumina. Zinc chloride was dried under vacuum at 140 ^oC for overnight and stored in the glovebox. Magnesium powder and anhydrous lithium chloride were stored in the glovebox when received. Commercially available reagents were used without further purification unless otherwise stated. Phosphines and palladium sources were stored in the glovebox.

Instrumentation:

HPLC analyses were performed using a Shimadzu Prominence system with SIL-20A auto sample, CTO-20AC column oven, LC-20AD pump system, DGU-20A3 degasser and SPD M20A Diode Array or UV/VIS detector. The following chiral columns from Daicel Chemical Industries were used: OJ-H (chiralcel), IC (chiralpak), AD-H (chiralpak) and IA (chiralpak) in 4.6 x 250 mm size.

GC-MS analyses were performed on a Shimadzu QP2010 apparatus using a RTx®-5ms column lined with a mass (EI 0.86 kV) detection system. All GC analyses were performed on an Shimadzu GC-2010 with a FID detector using an achiral column (Restek, **Rtx-1701**, 30 m, 0.25 mm, 0.25 μm, 14% Cyanopropylphenyl-86% dimethylpolysiloxane, T_{max} = 250 °C).

^{1}H, ^{13}C , ^{19}F and ^{31}P NMR spectra were recorded on BrukerAvance III (500 MHz) and BrukerAvance III (400 MHz) spectrometers at 298 K in $CDCl_3$ (residual peaks ^{1}H δ 7.26 ppm, ^{13}C δ 77.16 ppm) or Acetone-*d*$_6$ (^{1}H δ 2.05 ppm, ^{13}C δ 206.26 ppm). ^{19}F NMR spectra were referenced to external $CFCl_3$. All ^{31}P NMR spectra were reported in ppm relative to H_3PO_4 (0 ppm – external standard). Chemical shifts (δ) are reported in ppm relative to tetramethylsilane (0.00 ppm). Data is reported as follows: chemical shift in parts per million (ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and brs = broad), integration value, coupling constant in Hz if applicable.

High resolution mass spectrometry was recorded by Dr. H. Nadig and Dr. M. Pfeffer of the University of Basel on a Bruker maXis 4G QTOF ESI mass spectrometer.

Infrared spectra were measured on a ATR Varian Scimitar 800 FT-IR spectrometer and reported in cm^{-1}.

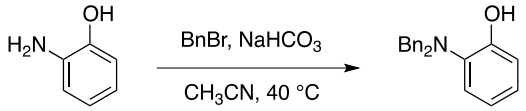
Optical rotations were measured on a Perkin Elmer 341 Polarimeter in a 1 mL micro cuvette (cell length 100mm) with NaD-Line (λ = 589 nm) at 20 °C.

2. Chapter 2: Terminal-selective functionalization of alkyl chains by regioconvergent cross-coupling

Synthesis of Aryl triflates

Unless otherwise noted, aryl triflates were prepared according to the procedure of Goossen *et al.*.[110]

<u>*N*-dibenzylphenyltriflate 2-12o</u>



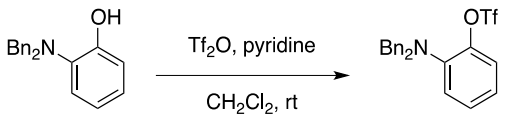
Prepared according to literature procedure.[111] A mixture of 2-aminophenol (1.09 g, 10 mmol), benzyl bromide (3.42 g, 20 mmol, 2 equiv.) and sodium bicarbonate (3.36 g, 40 mmol, 4 equiv.) in acetonitrile (150 mL) was stirred at 40 °C for 6 h. After cooling to room temperature, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. Water (100 mL) and ethyl acetate (100 mL) were added to the residue. Organic layer was separated, washed with water, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was passed through a plug of silica (pentane/CH_2Cl_2 60:40) to give 2-(dibenzylamino)phenol as a thick pale yellow oil (2.7 g, 93%).

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 – 7.22 (m, 5H), 7.22 – 7.16 (m, 4H), 7.16 – 7.11 (m, 1H), 7.08 – 6.98 (m, 2H), 6.87 – 6.78 (m, 2H), 4.02 (s, 4H);

^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 152.5, 137.6, 136.9, 129.3, 128.5, 127.6, 126.9, 124.0, 119.8, 114.1, 59.0;

IR (neat): ν (cm^{-1}) 3345, 3027, 1491, 1250, 758;

HRMS (ESI): Calcd for $C_{20}H_{20}NO$ ($[M+H]^+$): 290.1545, found 290.1540.



Prepared according to literature.[110] A solution of trifluoromethanesulfonic anhydride (0.82 mL, 4.84 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise to a solution of pyridine (0.56 mL, 6.92 mmol) and the corresponding phenol (1 g, 3.46 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0

°C. After complete addition, the mixture was warmed to room temperature and allowed to stir for 1 h. The mixture was then diluted with Et_2O (30 mL), quenched with 10 % aq. HCl and washed successively with sat. $NaHCO_3$ and brine. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was passed through a plug of silica (pentane/CH_2Cl_2 80:20) to give the desired aryl triflate **2-12o** as a colourless oil (1.5 g, quant.).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.25 (m, 6H), 7.25 – 7.15 (m, 6H), 7.07 (td, *J* = 7.8, 1.6 Hz, 1H), 6.92 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.16 (s, 4H);

^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 144.8, 143.8, 136.6, 129.4, 128.8, 128.4, 127.5, 124.2, 123.7, 122.2, 55.1;

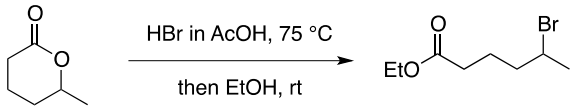
^{19}F-{^{1}H} NMR ($CDCl_3$, 376 MHz) δ -74.51;

IR (neat): ν (cm^{-1}) 2956, 1415, 1194, 1135, 884, 755, 701, 628;

HRMS (ESI): Calcd for $C_{21}H_{19}F_3NO_3S$ ($[M+H]^+$): 422.1038, found 422.1032.

Synthesis of alkyl bromides

Ethyl 5-bromohexanoate 2-13g

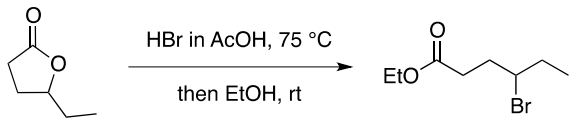


This compound was synthesized by a modified literature procedure.[112]

δ-Hexalactone (1.0 g, 8.76 mmol) was added to a flask containing a solution of 33% HBr in AcOH (3 mL) and fitted with a reflux condenser. The reaction was heated to 75 °C for 4 hours then cooled to room temperature, at which point ethanol (8.0 mL) was added and the mixture was stirred at room temperature overnight. The reaction was then partially concentrated under reduced pressure, taken up in EtOAc, washed three times with a saturated aqueous solution of sodium bicarbonate, brine, and the organic layer was dried with magnesium sulfate and concentrated under reduced pressure. The crude product was passed through a plug of silica (10% Et_2O/Pentane) to isolate methyl 5-bromohexanoate **2-13g** as a colourless liquid (1.5 g, 78% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.30 – 3.90 (m, 3H), 2.50 – 2.12 (m, 2H), 1.93 – 1.74 (m, 4H), 1.71 (d, *J* = 6.7 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H). The spectral data is consistent with that reported in the literature (*4*).

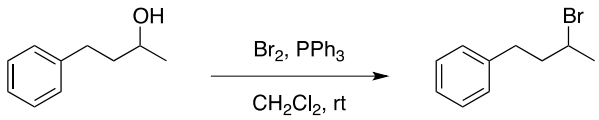
Ethyl 4-bromohexanoate 2-13h



This compound was synthesized from γ-caprolactone *via* lactone opening with HBr using a method identical to the one described for ethyl 5-bromohexanoate above to give the desired product **2-13h** as a colourless liquid (1.16 g, 59%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.1 Hz, 2H), 4.05 – 3.96 (m, 1H), 2.64 – 2.41 (m, 2H), 2.25 – 2.12 (m, 1H), 2.11 – 1.99 (m, 1H), 1.94 – 1.81 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.05 (t, *J* = 7.3 Hz, 3H). The spectral data is consistent with that reported in the literature.[111]

(3-Bromobutyl)benzene 2-13k

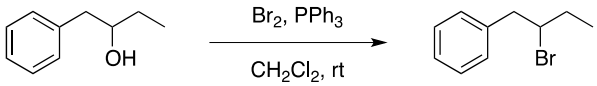


This compound was prepared according to the procedure of Denmark *et al*..[84]

Bromine (1.92 g, 0.62 mL, 12.0 mmol, 1.2 equiv) was added dropwise to a stirred suspension of triphenylphosphine (3.15 g, 12.0 mmol, 1.2 equiv) in CH_2Cl_2 (30 mL) in a round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of 4-phenyl-2-butanol (1.5 g, 10.0 mmol, 1.0 equiv) and imidazole (0.82 g, 12.0 mmol, 1.2 equiv) in CH_2Cl_2 (20 mL) was added dropwise. The cooling bath was removed, and the reaction mixture was allowed to warm to rt for 17 h. The mixture was then filtered on celite and concentrated in vacuo to leave a yellow oil residue. The latter was finally passed through a plug of silica (pentane) to give (3-bromobutyl)benzene **2-13k** as a colourless oil (1.9 g, 89%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 4.20 – 3.96 (m, 1H), 2.94 – 2.81 (m, 1H), 2.81 – 2.66 (m, 1H), 2.26 – 1.98 (m, 2H), 1.73 (d, *J* = 6.7 Hz, 3H). The spectral data is consistent with that reported in the literature.[84]

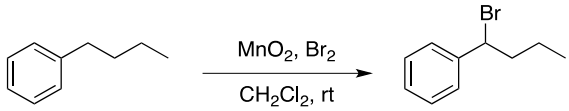
(2-Bromobutyl)benzene 2-13j



This compound was synthesized from 1-phenylbutan-2-ol using the same procedure as the one described above to give the desired compound **2-13j** as clear colourless oil (1.05 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.25 (m, 1H), 7.24 – 7.19 (m, 2H), 4.28 – 4.09 (m, 1H), 3.29 – 3.08 (m, 2H), 1.99 – 1.85 (m, 1H), 1.85 – 1.70 (m, 1H), 1.08 (t, *J* = 7.2 Hz, 3H). The spectral data are consistent with those reported in the literature.[113]

(1-Bromobutyl)benzene 2-13l

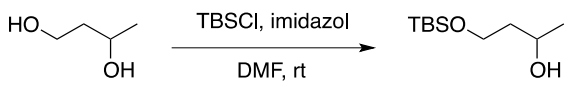


This compound was synthesized using the procedure of Li *et al*..[67]

Butylbenzene (1.34g, 10 mmol, 2.0 equiv.) and bromine (0.26 mL, 0.8 g, 5.0 mmol, 1.0 equiv.) were added to a round-bottom flask containing MnO_2 (85%, 1.02 g, 20 mmol, 2.0 equiv.) and dichloromethane (10 mL). The reaction mixture was then allowed to stir at room temperature until the disappearance of bromine color. The mixture was filtered and the filtrate was washed with water. The combined organic phases were dried over $MgSO_4$. The residue was then distilled to afford the pure (1-bromobutyl)benzene **2-13l** as a colourless oil (1.0 g, 93%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 2H), 7.29 – 7.24 (m, 2H), 7.23 – 7.17 (m, 1H), 4.94 – 4.87 (m, 1H), 2.28 – 1.98 (m, 2H), 1.49 – 1.38 (m, 1H), 1.32 – 1.22 (m, 1H), 0.87 (t, *J* = 7.4 Hz, 3H). The spectral data is consistent with that reported in the literature.[67]

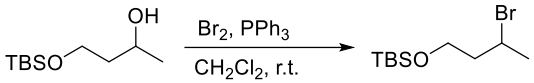
3-(Bromobutoxy)-*tert*-butyldimethylsilane 2-13i



The above compound was prepared according to a literature procedure.[114]

1,3-Butanediol (1.35 g, 15 mmol, 1 equiv.) and imidazole (2.25 g, 33 mmol, 2.2 equiv.) were stirred in DMF (7.5 mL) for 1 h at 0 °C. TBSCl (2.25 g, 15 mmol, 1 equiv.) was then added and the reaction mixture was allowed to warm to room temperature over 18 h. The reaction mixture was quenched with water and extracted with diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude product on silica gel (elution using Pentane/EtOAc: 85:15) furnished 4-(*tert*-butyldimethylsiloxy)butan-2-ol as a colourless oil (2.35 g, 77%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 – 3.98 (m, 1H), 3.93 – 3.77 (m, 2H), 3.39 (brs, 1H), 1.69 – 1.59 (m, 2H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H). The spectral data is consistent with that reported in the literature.[114]



The desired 3-(bromobutoxy)-*tert*-butyldimethylsilane **2-13i** was finally obtained, using the same procedure as for **2-13k**, as a colourless oil (1.83 g, 70%).

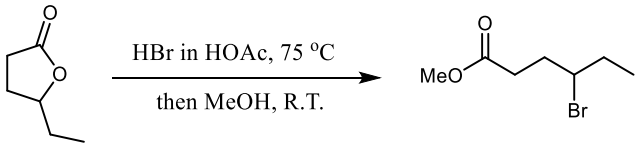
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.40 – 4.24 (m, 1H), 3.75 (t, *J* = 5.8 Hz, 2H), 2.01 – 1.92 (m, 2H), 1.74 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 61.1, 48.5, 44.0, 26.8, 26.1, 18.4, -5.2;

IR (neat): ν (cm^{-1}) 2954, 2929, 2857, 1678, 1418, 1254, 1183, 899, 832, 775, 704, 665, 536;

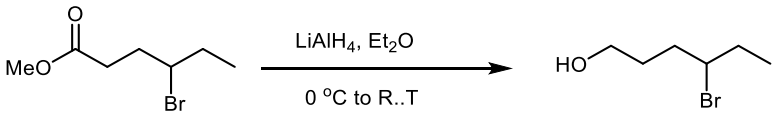
GCMS (EI) m/z for $C_{10}H_{23}BrOSi$ ($[M]^{+\bullet}$): 266.

<u>((4-bromohexyl)oxy)(*tert*-butyl)dimethylsilane 2-13m</u>

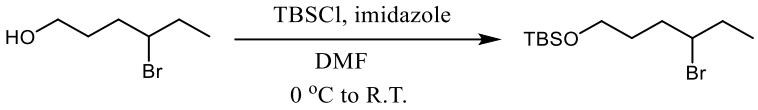


This compound was synthesized via lactone opening with HBr using a method identical to the one described for ethyl 5-bromohexanoate **2-13g** to furnish methyl 4-bromohexanoate as a clear liquid (4.50 g, 61%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.08 - 3.93 (m, 1H), 3.68 (s, 3H), 2.66 - 2.45 (m, 2H), 2.23 - 1.99 (m, 2H), 1.93 - 1.80 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H). The spectral data are consistent with those reported in the literature.[115]



A solution of lithium aluminum hydride (22.5 mL, 22.5 mmol, 1.0 M in Et_2O) was added dropwise to a 0 °C solution of methyl 4-bromohexanoate (3.01g, 14.4 mmol) in Et_2O (60 mL). The reaction was allowed to reach room temperature and stirred for 7 hours until TLC showed complete consumption of the starting material. The reaction was quenched by the sequential slow addition of water, 2.5M NaOH solution, and water. The insoluble salts were removed via suction filtration. The mixture was extracted with Et_2O. The organic phase was separated and dried and then evaporated to give the product which was used for the next step without further purification.[66]



The above alcohol (1.81g, 10 mmol) and imidazole (1.50g, 22 mmol) were stirred in DMF (5.0 mL) for 1 h at 0 °C. TBSCl (1.51g, 10 mmol) was then added and the reaction mixture was allowed to r.t. over 18 h. The reaction mixture was quenched with water and extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (elution with Pentane) to afford **2-13m** as a pale yellow oil (1.59 g, 54% yield).

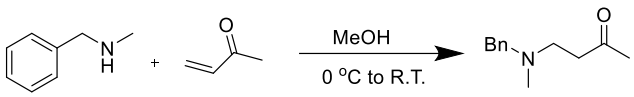
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.07 - 3.97 (m, 1H), 3.68 - 3.59 (m, 2H), 1.99 - 1.75 (m, 5H), 1.70 - 1.58 (m, 1H), 1.04 (t, *J* = 7.3 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 62.5, 60.5, 35.4, 32.4, 30.9, 26.1, 18.5, 12.2, -5.2;

IR (neat): ν (cm^{-1}) 2953, 2928, 2885, 2856, 1471, 1462, 1405, 1383, 1254, 1097, 961, 836, 776, 715, 661;

HRMS (ESI): Calcd for $C_{12}H_{27}BrNaOSi$ ($[M+Na]^+$): 317.0912, found 317.0903.

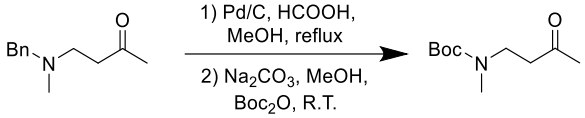
***tert*-Butyl (3-bromobutyl)(methyl)carbamate 2-13n**



The above compound was prepared according to literature procedure.[116]

To a solution of but-3-en-2-one (4.2 g, 60 mmol) in absolute MeOH (30 mL) at 0 °C, was added *N*-methyl-1-phenylmethanamine (6.61 g, 54.5 mmol) dropwise via syringe. The mixture was warmed to room temperature and was stirred for 2 h until complete consumption of the starting material. The solvent was removed under reduced pressure to give a brown oil. Purification by flash chromatography on silica gel (elution Pentane/EtOAc: 2/1) provided the desired product as a light brown oil (9.37 g, 90%).

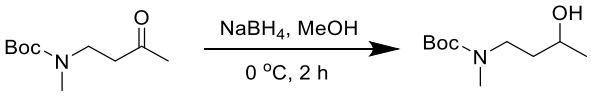
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 – 7.18 (m, 5H), 3.45 (s, 2H), 2.70 – 2.65 (m, 2H), 2.62 – 2.56 (m, 2H), 2.15 (s, 3H), 2.10 (s, 3H). The spectral data is consistent with that reported in the literature.[116]



The above compound was prepared according to literature procedure.[116]

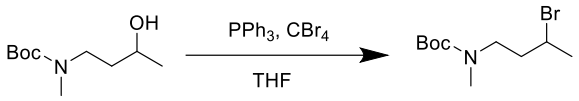
To a solution of 4-(benzyl(methyl)amino)butan-2-one (3.06 g, 16.0 mmol) in absolute MeOH (80 mL) at 0 °C, was added formic acid (8.0 mL) and palladium black (231 mg, 5%). The resulting suspension was heated to reflux under argon for 1 h until complete consumption of the starting material. The catalyst was filtered through Celite and washed with methanol (2×5 mL). To the filtrate at 0 °C, was added sodium carbonate (5.09 g, 48 mmol) and Boc_2O (6.29 g, 28.0 mmol) and the stirred reaction mixture was warmed to room temperature. After 1 h, MeOH was removed under reduced pressure and the residue was extracted with ethyl acetate (3×50 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated to provide a colourless oil. Purification by flash chromatography on silica gel (elution Pentane/EtOAc: 4/1) provided the desired product as a colourless oil (2.57 g, 80% for 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (t, *J* = 6.5 Hz, 2H), 2.83 (s, 3H), 2.66 (brs, 2H), 2.15 (s, 3H), 1.43 (s, 9H). The spectral data is consistent with that reported in the literature.[116]



$NaBH_4$ (1.8 g, 47.5 mmol) was added to a solution of *tert*-butyl methyl(3-oxobutyl)carbamate (2.9 g, 14.4 mmol) in MeOH (80 mL) under an argon atmosphere and the reaction mixture was allowed to stir at 0 °C for 2 h. The solvent was removed under reduced pressure and the

residue was dissolved in Et_2O. The mixture was washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was used directly in the next step.



PPh_3 (7.4 g, 28.2 mmol) was added to a solution of *tert*-butyl (3-hydroxybutyl)(methyl)carbamate (1.83 g, 9 mmol) and CBr_4 (9.34g, 28.2 mmol) in 100 mL of dry THF. The reaction mixture was stirred under argon overnight. THF was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (elution from Pentane to Pentane/Et_2O 6/1) to afford the desired product **2-13n** as a yellow oil (1.19 g, 50%).

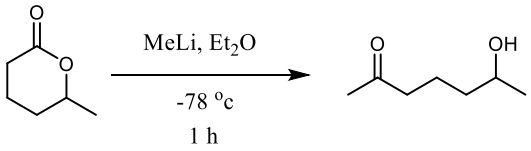
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.24 – 3.97 (m, 1H), 3.46 – 3.25 (m, 2H), 2.86 (s, 3H), 2.10 – 1.93 (m, 2H), 1.74 (d, *J* = 6.7 Hz, 3H), 1.45 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 79.7, 48.6, 47.6, 39.3, 34.8, 28.6, 26.7;

IR (neat): ν (cm^{-1}) 2972, 2926, 1691, 1455, 1392, 1365, 1243, 1158, 878, 772;

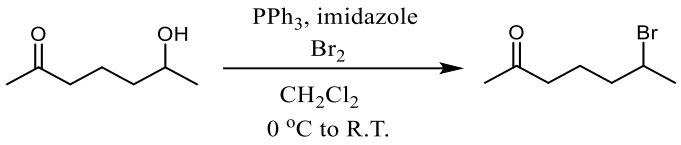
HRMS (ESI): Calcd for $C_{10}H_{20}BrNaNO_2$ ([M+Na]$^+$): 288.0575, found 288.0571.

2-(4-bromopentyl)-2-methyl-1,3-dioxolane 2-13o

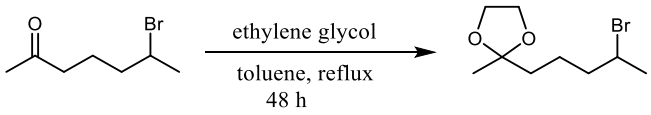


The above compound was prepared according to literature procedure.[117]

Under Argon, to a -78 ºC solution of delt-hexanolactone (2.28g, 20 mmol) in Et_2O (50 mL) was added a solution of MeLi (13.8 mL, 22 mmol, 1.6 M in Et_2O). The mixture was stirred at -78 ºC for 1 h. The reaction mixture was quenched by sat. NH_4Cl solution. After warming the mixture to room temperature, NaCl was added to saturate the solution. The product was extracted from the aqueous layer with copious amounts of Et_2O (Note: the product is extremely soluble in water phase). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give a colourless oil. The residue was used directly for the next step.



The above compound was synthesized using the same procedure as the one described for **2-13k** and gave 6-bromoheptan-2-one as clear oil (1.2 g, 31% yield over two steps).



To a solution of 6-bromoheptan-2-one (1.2 g, 6.21 mmol) in toluene (15.0 mL) was added ethylene glycol (0.77 g, 0.70 mL, 12.4 mmol) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (118 mg, 0.621 mmol). The reaction mixture was then stirred at reflux with a Dean-Stark over 48 h. The reaction mixture was cooled to room temperature, quenched by sat. sodium bicarbonate solution (10 mL) and then extracted with Et_2O (3 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude by column chromatography on silica gel (elution from pentane to pentane/Et_2O: 90/10) afforded **2-13o** as a colourless oil (1.2 g, 82% yield).

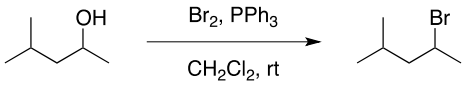
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 - 4.07 (m, 1H), 3.99 - 3.88 (m, 4H), 1.90 - 1.73 (m, 2H), 1.70 (d, J = 6.7 Hz, 3H), 1.67 - 1.56 (m, 3H), 1.55 - 1.46 (m, 1H), 1.31 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 110.0, 64.8, 64.8, 51.6, 41.3, 38.5, 26.6, 23.9, 22.5;

IR (neat): ν (cm^{-1}) 2982, 2952, 2877, 1447, 1376, 1196, 1148, 1045, 947, 871, 592, 533;

HRMS (ESI): Calcd for $C_9H_{18}BrO_2$ ($[M+H]^+$): 237.0490, found 237.0484.

<u>2-Bromo-4-methylpentane 2-13p</u>



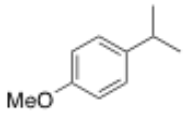
This compound was prepared from 4-methylpentan-2-ol using an identical procedure as for **2-13k**. The desired product **2-13p** was obtained as a colourless oil (2.0 g, 40%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 – 4.12 (m, 1H), 1.89 – 1.77 (m, 2H), 1.70 (d, *J* = 6.6 Hz, 3H), 1.56 – 1.43 (m, 1H), 0.92 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H). The spectral data is consistent with that reported in the literature.[118]

General procedure for the direct arylation of 2-bromopropane

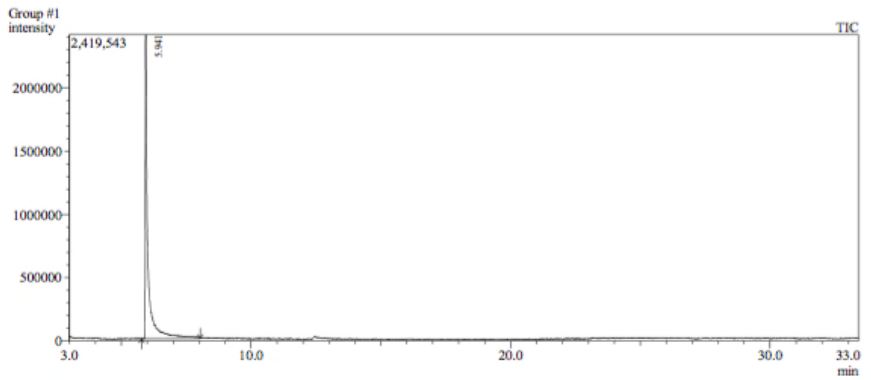
In an argon-filled glove box, a Pyrex glass tube with stir bar was charged with LiCl (85 mg, 2 mmol, 4 equiv.), Mg (49 mg, 2 mmol, 4 equiv.), $ZnCl_2$ (273 mg, 2 mmol, 4 equiv.), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 2.5 mol%) and **CPhos** (16.4 mg, 0.0375 mmol, 7.5 mol%). The tube was sealed with a septum and paraffin, and was taken out of the glove box. Under an argon atmosphere, THF (2.5 mL), *p*-methoxyphenyl trifluoromethanesulfonate (0.5 mmol) and 2-bromopropane (2 mmol, 4 equiv.) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 16 h in an aluminum block. After this time, an aliquot of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was measured by GCMS. Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated. The residue was subjected to column chromatography to yield the product as a mixture of linear/branched regioisomers (which could not be separated by column chromatography).

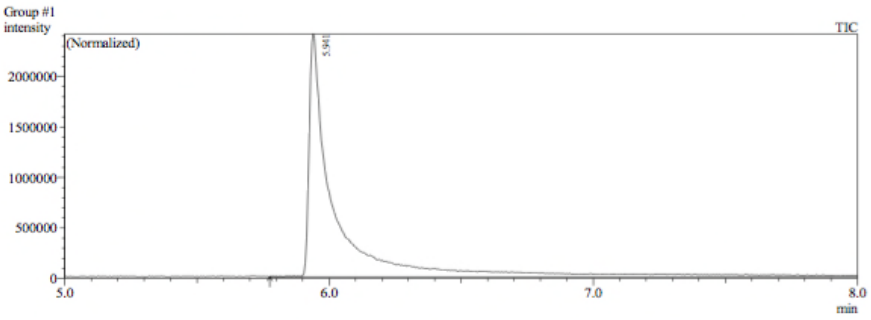
1-isopropyl-4-methoxybenzene 2-15a



The above compound was obtained according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and 2-bromopropane. The ratio between the regioisomers was determined by GCMS (branched/linear >99:1). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 90:10) gave 61.5 mg (82%) of product as a colourless oil.

*GCMS chromatogram of the crude reaction using **CPhos** as ligand*



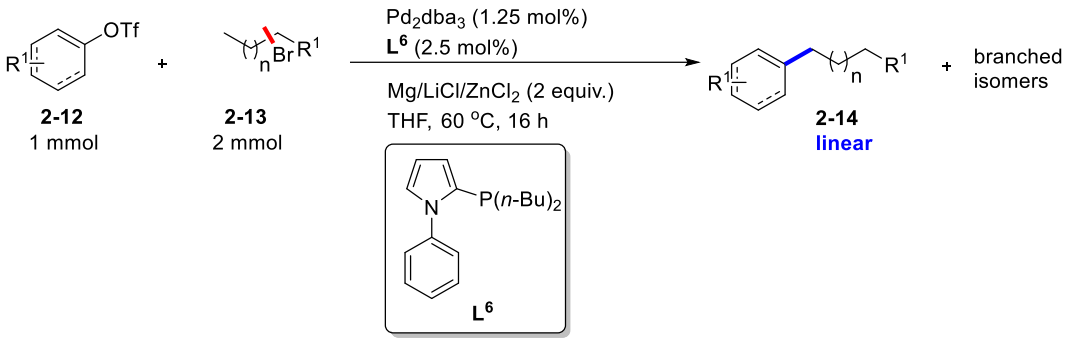


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	5.941	5.775	8.035	15933685	100.00	2399597	100.00	6.64	MI	
				15933685	100.00	2399597	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.81 (s, 3H), 2.95 – 2.83 (m, 1H), 1.25 (d, *J* = 6.9 Hz, 6H). The spectral data is consistent with that reported in the literature.[119]

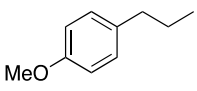
General procedure for the migrative cross-coupling reaction of aryl triflates and alkyl bromides



In an argon-filled glove box, a Pyrex glass tube with stir bar was charged with LiCl (85 mg, 2 mmol, 2 equiv.), Mg (49 mg, 2 mmol, 2 equiv.), $ZnCl_2$ (273 mg, 2 mmol, 2 equiv.), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 1.25 mol%) and phosphine **L^6** (7.2 mg, 0.025 mmol, 2.5 mol%). The tube was sealed with a septum and paraffin, and was taken out of the glove box. Under an argon atmosphere, THF (2.5 mL), the aryltriflate (1 mmol) and alkylbromide (2 mmol, 2 equiv.) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 16 h in an aluminum block. After this time, an aliquot of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was measured by GCMS. Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered through silica and concentrated. The residue was subjected to column chromatography to yield the product as a mixture of linear/branched regioisomers (which could not be separated by column chromatography).

Characterization data for the linear products

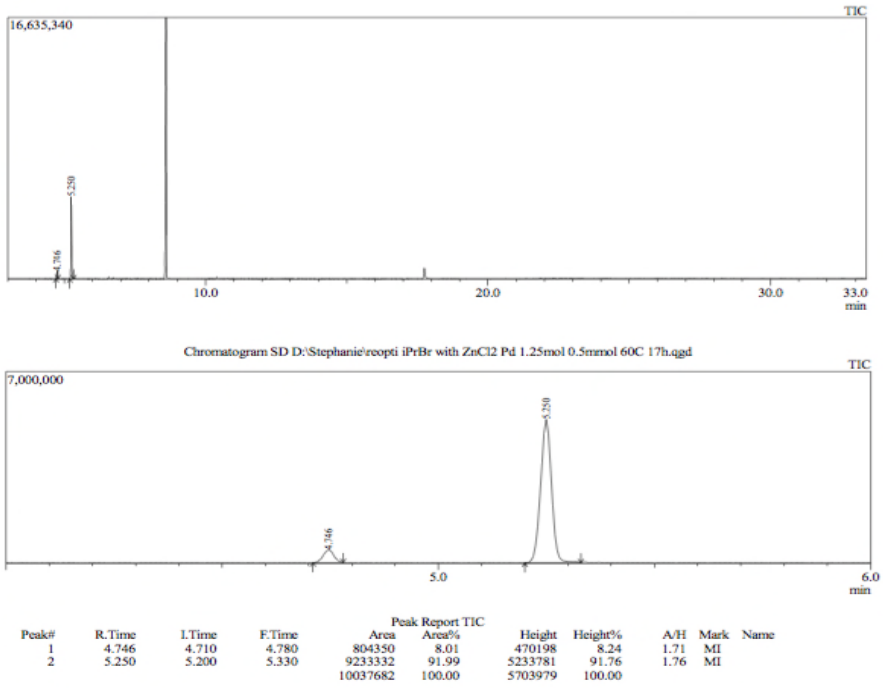
1-Methoxy-4-propylbenzene 2-14a



The above compound was obtained according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and 2-bromopropane. After completion, tetradecane was added to the crude mixture. The yield and ratio between the regioisomers was determined by GCMS (linear/branched 92:8). Purification by column chromatography on

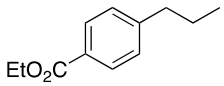
silica gel (elution from pentane to pentane/CH_2Cl_2 89:11) gave 60 mg (80%) of the mixture of regioisomers as yellow oil.[119, 120]

GCMS chromatogram of the crude mixture



^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13-7.06 (m, 2H), 6.86-6.80 (m, 2H), 3.79 (s, 3H), 2.53 (t, *J* = 7.6 Hz, 2H), 1.57-1.67 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). The spectral data is consistent with that reported in the literature.[120]

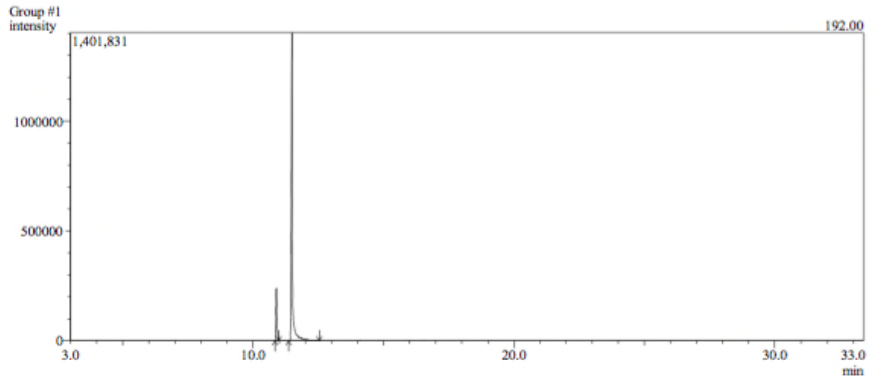
Ethyl 4-propylbenzoate

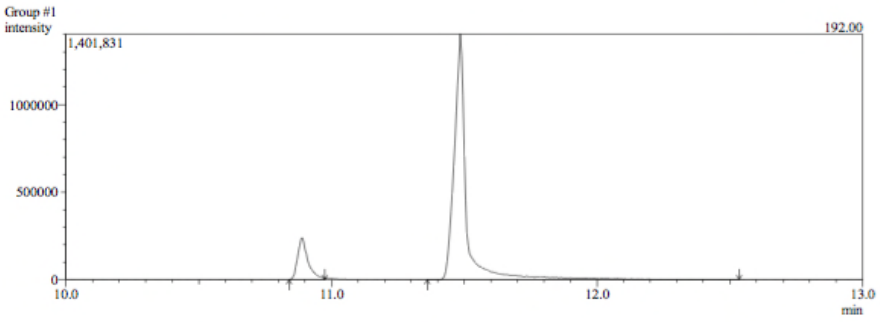


The above compound was synthesized according to the general procedure from ethyl 4-(trifluoromethylsulfonyloxy)benzoate and 2-bromopropane **2-13a** using Mg powder (4 equiv.), LiCl (4 equiv.), $ZnCl_2$ (4 equiv.), Pd_2dba_3 (2.5 mol%) and phosphine **L^6** (5 mol%). The ratio between the regioisomers was determined by GCMS (linear/branched 87:13). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 55:45) gave 146 mg (76%) of the mixture of regioisomers as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.64 (t, *J* = 7.3 Hz, 2H), 1.72 – 1.60 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H). The spectral data is consistent with that reported in the literature.[121]

GCMS chromatogram of the crude mixture

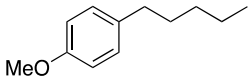




Peak Report192

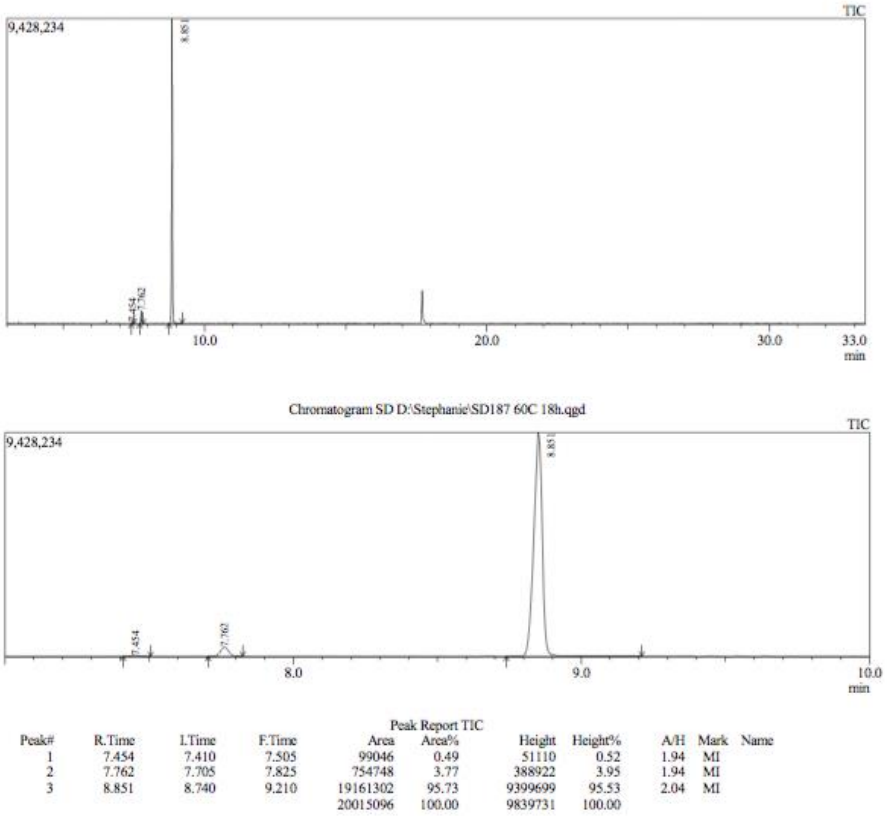
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	10.889	10.840	10.975	644224	12.86	239378	14.59	2.69	MI	
2	11.485	11.360	12.535	4364993	87.14	1401349	85.41	3.11	MI	
				5009217	100.00	1640727	100.00			

1-methoxy-4-pentylbenzene 2-14a'



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and 1-bromopentane (**2-13f**). The ratio between the regioisomers was determined by GCMS (linear/branched 96:4). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 85:15) gave 146 mg (82%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture:



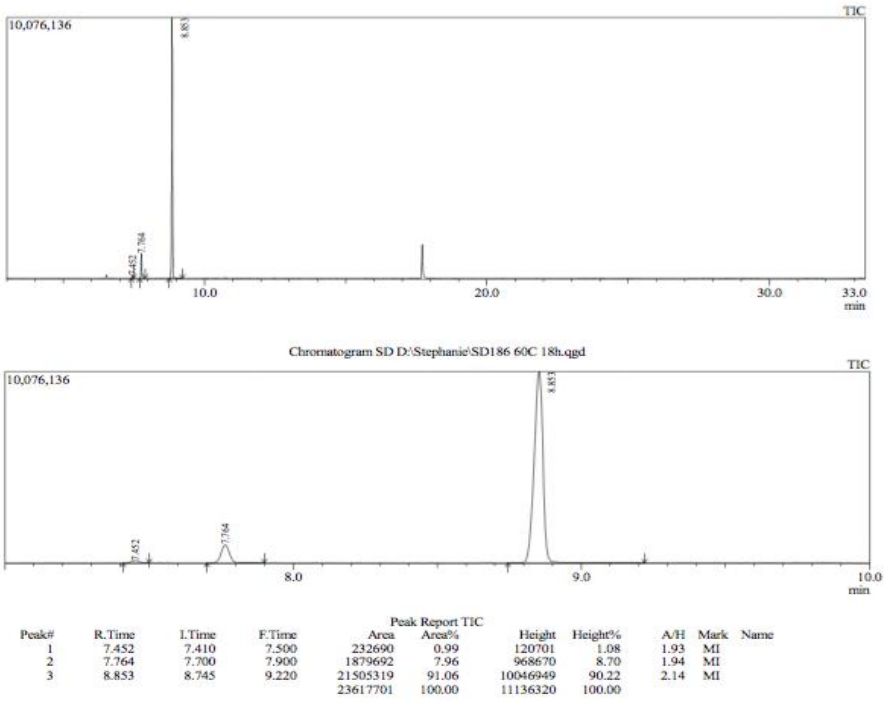
Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	7.454	7.410	7.505	99046	0.49	51110	0.52	1.94	MI	
2	7.762	7.705	7.825	754748	3.77	388922	3.95	1.94	MI	
3	8.851	8.740	9.210	19161302	95.73	9399699	95.53	2.04	MI	
				20015096	100.00	9839731	100.00			

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13-7.07 (m, 2H), 6.85-6.80 (m, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 1.63-1.53 (m, 2H), 1.39-1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). The spectral data is consistent with that reported in the literature.[122]

From 2-bromopentane (**2-13e**): The ratio between the regioisomers was determined by GCMS (linear/branched 91:9). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 85:15) gave 155 mg (87%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

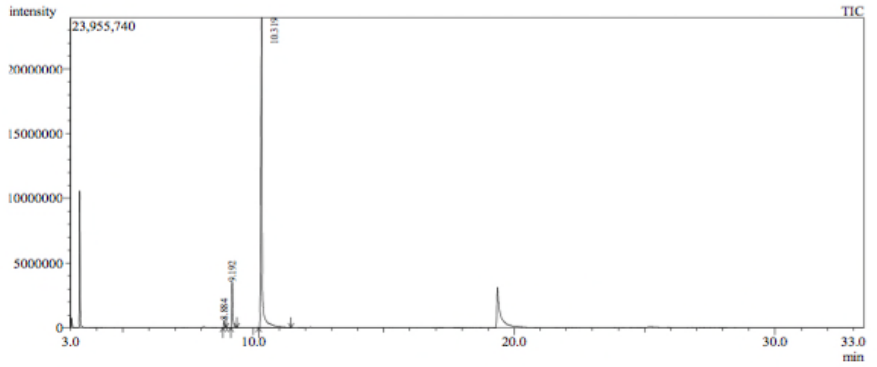


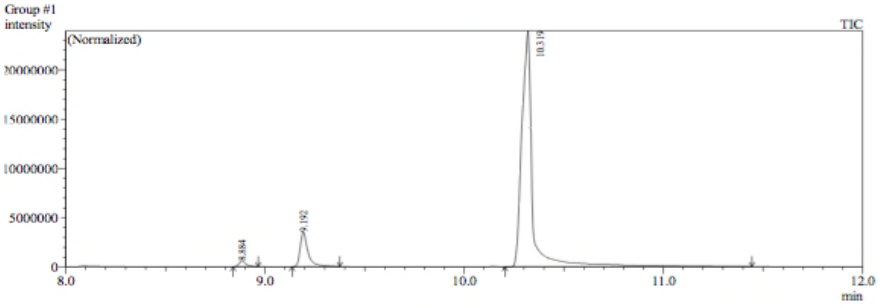
Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	7.452	7.410	7.500	232690	0.99	120701	1.08	1.93	MI	
2	7.764	7.700	7.900	1879692	7.96	968670	8.70	1.94	MI	
3	8.853	8.745	9.220	21505319	91.06	10046949	90.22	2.14	MI	
				23617701	100.00	11136320	100.00			

From 3-bromopentane (**2-13d**): The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 85:15) gave 141 mg (79%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

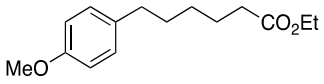




Peak Report TIC

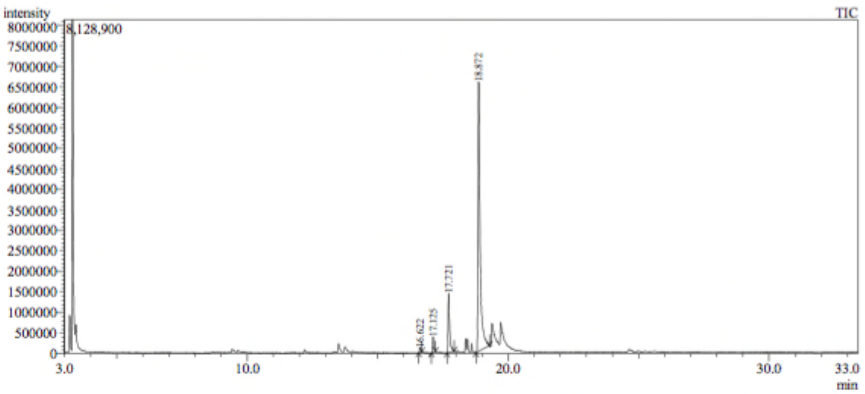
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	8.884	8.840	8.965	1330475	1.33	562500	2.01	2.37	MI	
2	9.192	9.135	9.375	9589333	9.61	3493095	12.48	2.75	MI	
3	10.319	10.205	11.445	88867671	89.06	23926479	85.51	3.71	MI	
				99787479	100.00	27982074	100.00			

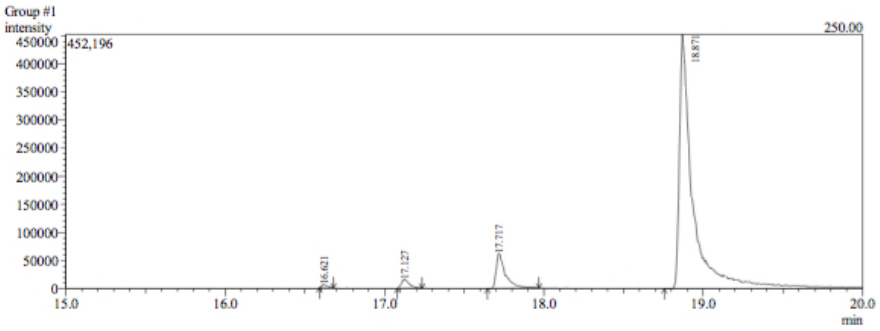
Ethyl 6-(4-methoxyphenyl)hexanoate 2-14x



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and ethyl 5-bromohexanoate (**2-13g**). The ratio between the regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 89:11) gave 185 mg (74%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





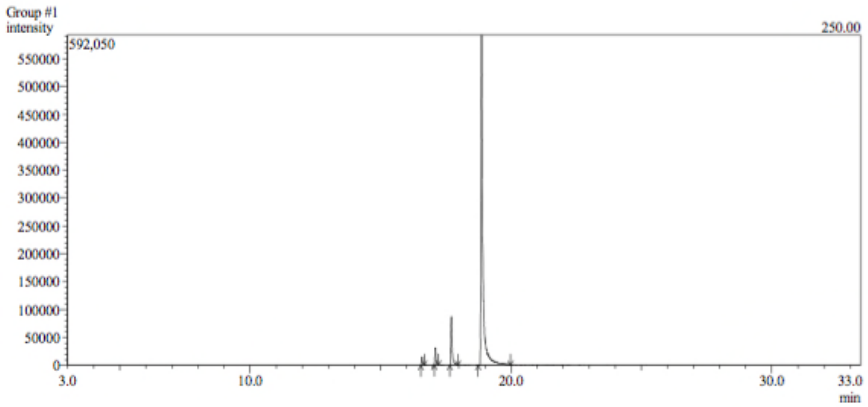
Peak Report 250

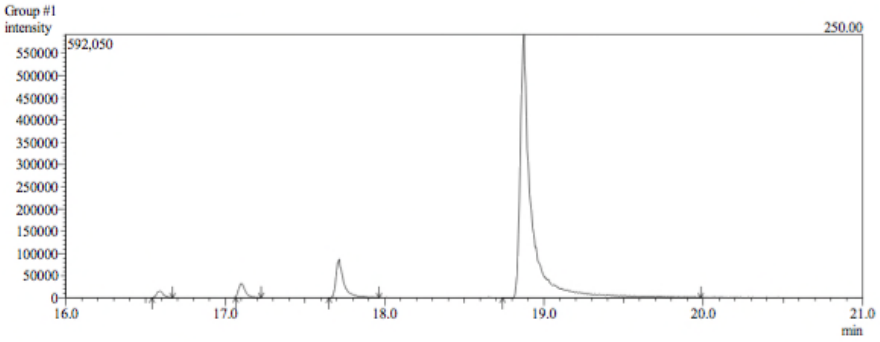
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	16.621	16.590	16.680	15654	0.52	6473	1.20	2.42	MI	
2	17.127	17.080	17.235	54220	1.81	16747	3.12	3.24	MI	
3	17.717	17.645	17.970	247819	8.30	62370	11.60	3.97	MI	
4	18.871	18.755	20.450	2669853	89.37	451923	84.08	5.91	MI	
				2987546	100.00	537513	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.06 (m, 2H), 6.85 – 6.80 (m, 2H), 4.12 (q, *J* = 7.2 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.3 Hz, 2H), 2.28 (t, *J* = 7.8 Hz, 2H), 1.69 – 1.57 (m, 4H), 1.39 – 1.32 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H). The spectral data is consistent with that reported in the literature.[123]

From ethyl 4-bromohexanoate (**2-13h**): The ratio between the regioisomers was determined by GCMS (linear/branched 87:13). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 89:11) gave 173 mg (69%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

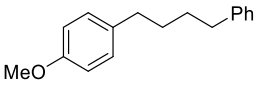




Peak Report 250

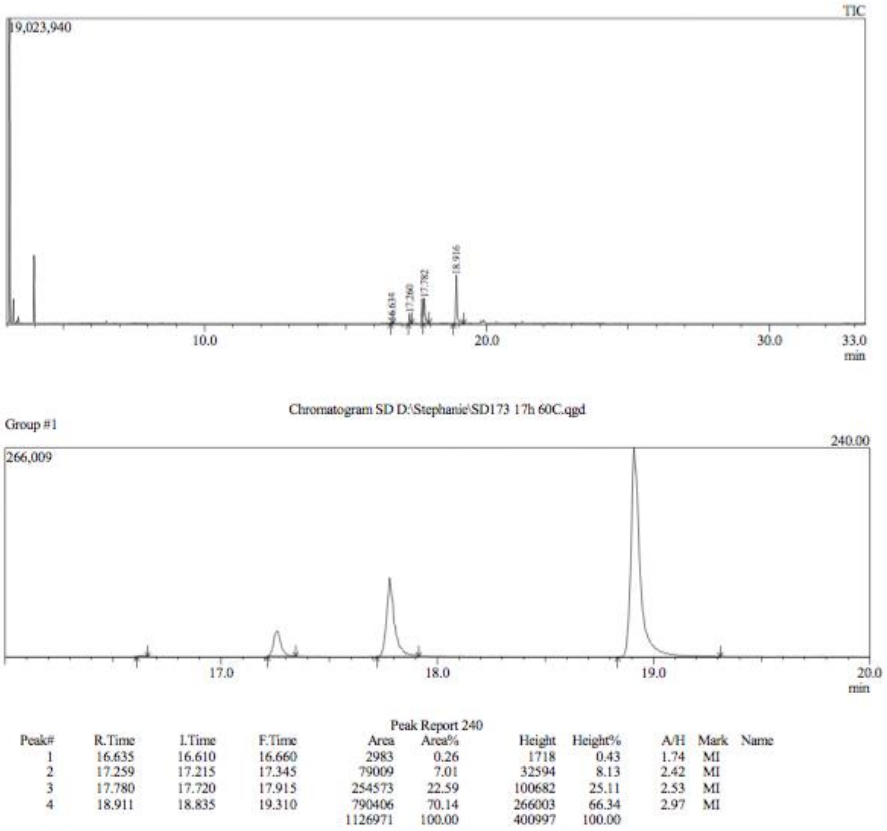
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	16.589	16.540	16.670	47040	1.42	15624	2.15	3.01	MI	
2	17.096	17.065	17.225	92913	2.81	31448	4.33	2.95	MI	
3	17.714	17.650	17.965	299979	9.08	87624	12.06	3.42	MI	
4	18.874	18.740	19.985	2863205	86.68	591734	81.46	4.84	MI	
				3303137	100.00	726430	100.00			

1-(*p*-Methoxyphenyl)-4-phenylbutane 2-14z



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-13a**) and 3-(bromobutyl)benzene (**2-13k**). The ratio between the regioisomers was determined by GCMS (linear/branched 70:30). Purification by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 65:35) gave 153 mg (64%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



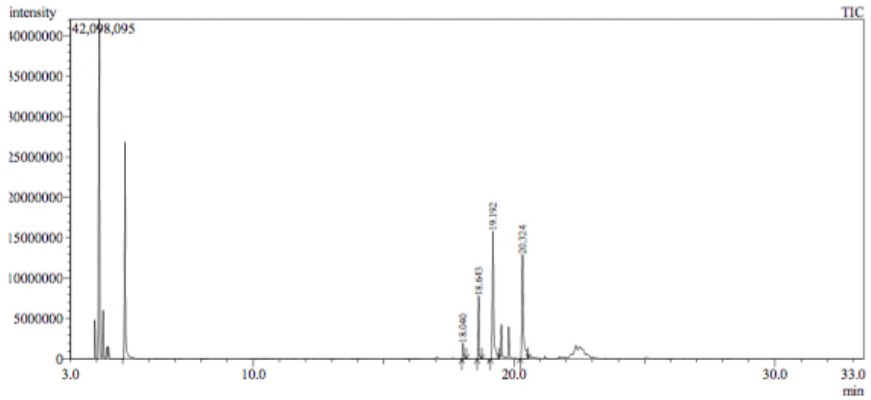
Peak Report 240

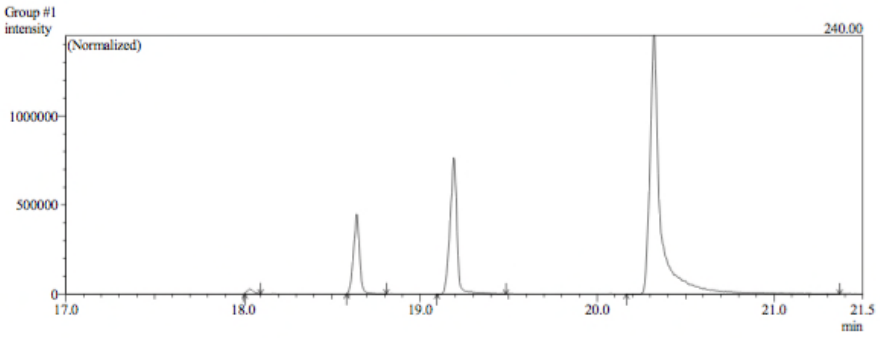
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	16.635	16.610	16.660	2983	0.26	1718	0.43	1.74	MI	
2	17.259	17.215	17.345	79009	7.01	32594	8.13	2.42	MI	
3	17.780	17.720	17.915	254573	22.59	100682	25.11	2.53	MI	
4	18.911	18.835	19.310	790406	70.14	266003	66.34	2.97	MI	
				1126971	100.00	400997	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29 – 7.24 (m, 2H), 7.20 – 7.15 (m, 3H), 7.10 – 7.06 (m, 2H), 6.84 – 6.79 (m, 2H), 3.78 (s, 3H), 2.63 (t, *J* = 7.2 Hz, 2H), 2.58 (t, *J* = 7.1 Hz, 2H), 1.67 – 1.61 (m, 4H). The spectral data are consistent with those reported in the literature.[124]

From 2-(bromobutyl)benzene (**2-13j**). The ratio between the regioisomers was determined by GCMS (linear/branched 65:35). Purification by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 65:35) gave 140 mg (58%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

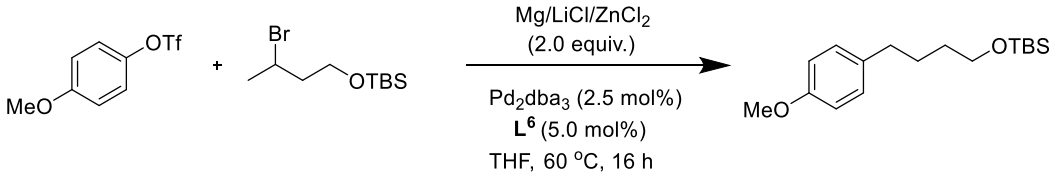




Peak Report 240

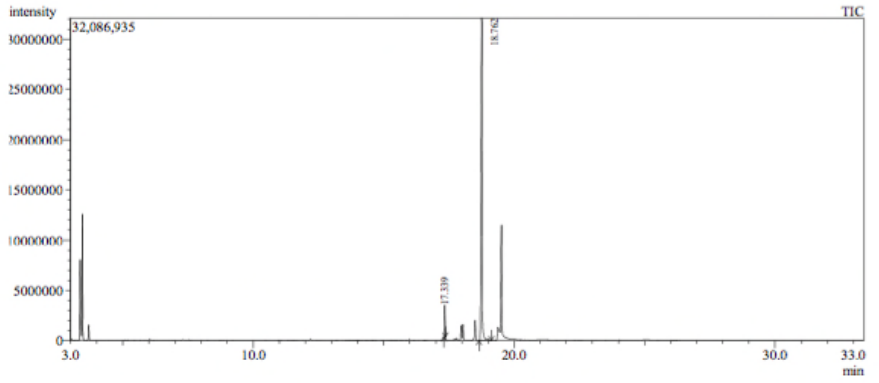
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	18.038	18.010	18.100	65963	0.70	26146	0.97	2.52	MI	
2	18.642	18.585	18.810	1052806	11.23	445951	16.60	2.36	MI	
3	19.192	19.095	19.485	2130308	22.73	764762	28.47	2.79	MI	
4	20.322	20.165	21.370	6123314	65.33	1449116	53.95	4.23	MI	
				9372391	100.00	2685975	100.00			

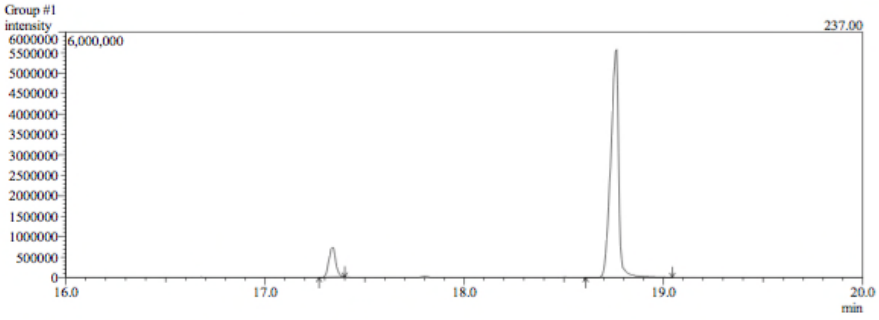
4-(4-Methoxyphenyl)butan-1-ol 2-14y



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and 3-(bromobutoxy)-*tert*-butyldimethylsilane (**2-13i**) using Pd_2dba_3 (0.025 mmol, 22.9 mg) and phosphine **L^6** (0.05 mmol, 14.4 mg). The ratio between the regioisomers was determined by GCMS (linear/branched 93:7). The reaction mixture was quenched with NH_4Cl (3 mL) and extracted twice with Et_2O (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered off and concentrated to dryness. The residue was directly used in the next step.

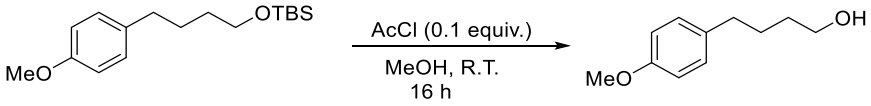
GCMS chromatogram of the crude mixture





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.339	17.305	17.370	6715620	6.78	3147282	8.94	2.13	MI	
2	18.762	18.650	19.125	92406389	93.22	32050105	91.06	2.88	MI	
				99122009	100.00	35197387	100.00			



Acetyl chloride (0.1 equiv.) was added dropwise to MeOH (50 mL) at 0 °C. This solution was next slowly added to the crude residue in MeOH (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 16 h. The crude mixture was concentrated to dryness and the residue was filtered on silica (pentane/Et_2O 60:40) to furnish 148 mg (82% for 2 steps) of **2-14y** as a thick oil.

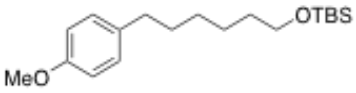
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 – 7.08 (m, 2H), 6.85 – 6.81 (m, 2H), 3.79 (s, 3H), 3.66 (t, *J* = 6.3 Hz, 2H), 2.59 (t, *J* = 7.4 Hz, 2H), 1.72 – 1.56 (m, 4H);

^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 157.9, 134.6, 129.4, 113.9, 63.0, 55.4, 34.9, 32.5, 27.9;

IR (neat): ν (cm^{-1}) 3335, 2918, 2850, 1511, 1492, 1244, 1035;

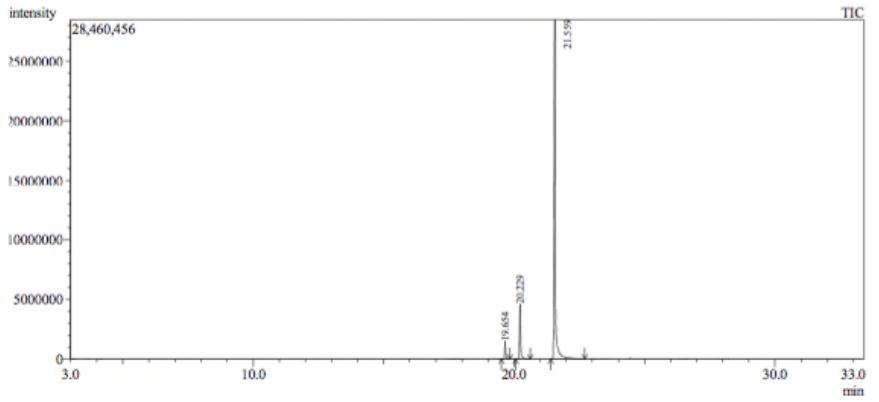
HRMS (ESI): Calcd for $C_{11}H_{16}NaO_2$ ([M+Na]$^+$): 203.1048, found 203.1040.

***tert*-Butyl((6-(4-methoxyphenyl)hexyl)oxy)dimethylsilane 2-14aa**



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and ((4-bromohexyl)oxy)(*tert*-butyl)dimethylsilane (**2-13m**) using Pd_2dba_3 (0.025 mmol, 22.9 mg) and phosphine **L**[6] (0.05 mmol, 14.4 mg). The ratio between the regioisomers was determined by GCMS (linear/branched 84:16). Purification by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 85:15) gave 170 mg (53%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the isolated regioisomers



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	19.654	19.515	19.845	4313080	3.89	1526085	4.41	2.83	MI	
2	20.229	20.060	20.625	13147323	11.85	4615808	13.35	2.85	MI	
3	21.559	21.405	22.710	93452497	84.26	28425969	82.23	3.29	MI	
				110912900	100.00	34567862	100.00			

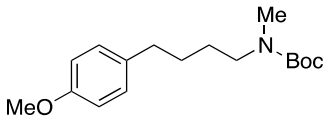
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 – 7.07 (m, 2H), 6.84 – 6.81 (m, 2H), 3.79 (s, 3H), 3.59 (t, *J* = 6.6 Hz, 2H), 2.60 – 2.49 (m, 2H), 1.60 – 1.49 (m, 4H), 1.37 – 1.31 (m, 4H), 0.90 (s, 9H), 0.04 (s, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 135.1, 129.4, 113.8, 63.4, 55.4, 35.1, 33.0, 31.9, 29.2, 26.1, 25.8, 18.5, -5.1;

IR (neat): ν (cm^{-1}) 2927, 2854, 1612, 1511, 1463, 1360, 1245, 1176, 1098, 1039, 834, 775;

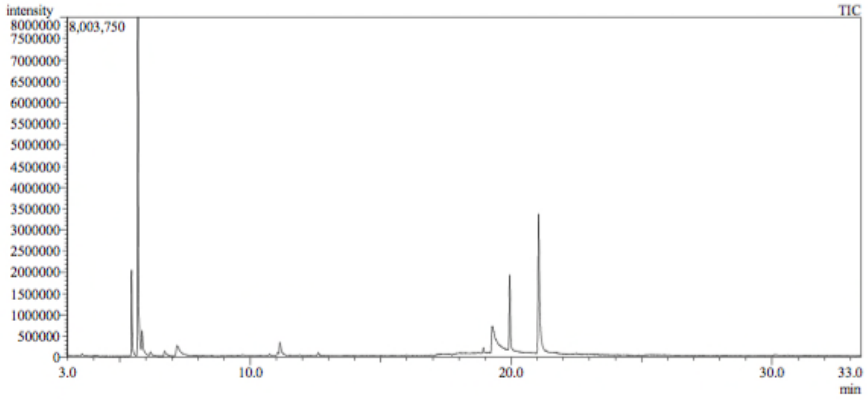
HRMS (ESI): Calcd for $C_{19}H_{34}NaO_2Si$ ($[M+Na]^+$): 345.2226, found 345.2222.

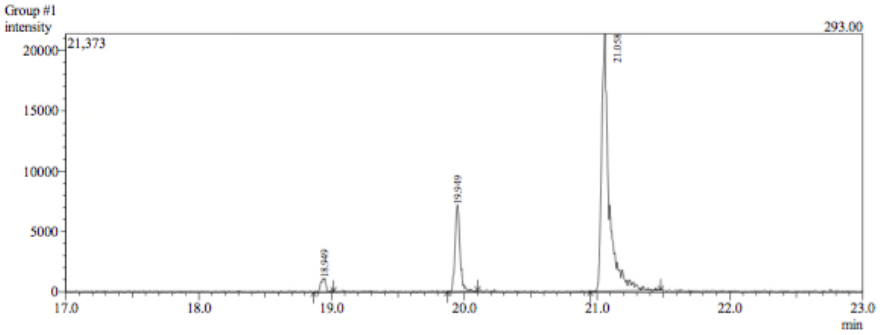
***tert*-Butyl (4-(4-methoxyphenyl)butyl)(methyl)carbamate 2-14ab**



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and *tert*-butyl (3-bromobutyl)(methyl)carbamate (**2-13n**) using Pd_2dba_3 (0.025 mmol, 22.9 mg) and phosphine **L^6** (0.05 mmol, 14.4 mg). The ratio between the regioisomers was determined by GCMS (linear/branched 80:20). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 6:1) gave 139 mg (48%) of the mixture of regioisomers as yellow oil.

GCMS chromatogram of the crude mixture





Peak Report 293

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	18.949	18.865	19.015	3014	2.87	1144	3.86	2.63	MI	
2	19.949	19.870	20.100	18388	17.50	7203	24.29	2.55	MI	
3	21.058	20.950	21.480	83667	79.63	21307	71.85	3.93	MI	
				105069	100.00	29654	100.00			

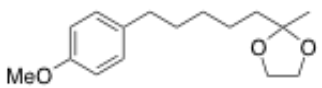
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.05 (m, 2H), 6.87 – 6.77 (m, 2H), 3.78 (s, 3H), 3.21 (brs, 2H), 2.81 (s, 3H), 2.57 (t, *J* = 7.2 Hz, 2H), 1.63 – 1.49 (m, 4H), 1.44 (s, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 155.8, 129.2, 127.7, 113.7, 79.1, 55.2, 48.7, 48.2, 47.4, 34.6, 34.0, 28.5;

IR (neat): ν (cm^{-1}) 2928, 1692, 1512, 1393, 1365, 1245, 1163;

HRMS (ESI): Calcd for $C_{17}H_{27}NNaO_3$ ($[M+Na]^+$): 316.1889, found 316.1885.

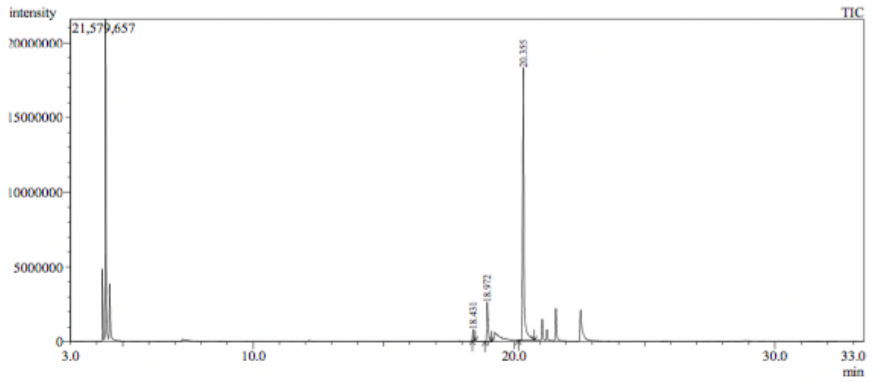
2-(5-(4-methoxyphenyl)pentyl)-2-methyl-1,3-dioxolane 2-14ac

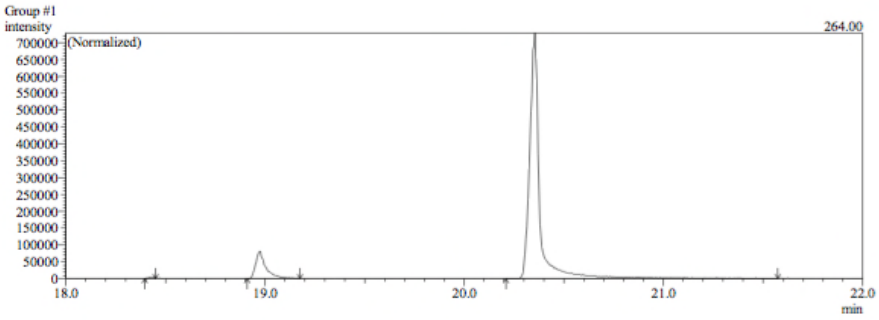


The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and 2-(4-bromopentyl)-2-methyl-1,3-dioxolane (**2-13o**). The ratio between the regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on

silica gel (elution from pentane to pentane/ Et_2O 90:10) gave 160 mg (61%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report 264

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	18.430	18.395	18.450	8234	0.29	4053	0.50	2.03	MI	
2	18.974	18.910	19.175	293286	10.31	82257	10.10	3.57	MI	
3	20.354	20.210	21.575	2542865	89.40	727900	89.40	3.49	MI	
				2844385	100.00	814210	100.00			

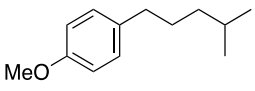
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.14 – 7.04 (m, 2H), 6.86 – 6.79 (m, 2H), 3.98 – 3.87 (m, 4H), 3.79 (s, 3H), 2.67 – 2.48 (m, 2H), 1.68 – 1.33 (m, 8H), 1.31 (s, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.8, 135.0, 129.4, 113.8, 110.3, 64.7, 55.4, 39.3, 35.1, 31.8, 29.6, 24.1, 23.9;

IR (neat): ν (cm^{-1}) 2981, 2929, 2854, 1611, 1511, 1376, 1300, 1241, 1066, 1037, 947, 828;

HRMS (ESI): Calcd for $C_{16}H_{24}NaO_3$ ($[M+Na]^+$): 287.1623, found 287.1621.

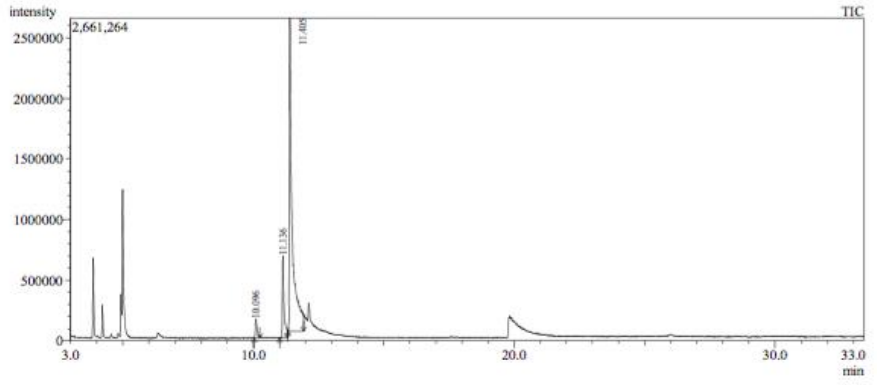
1-Methoxy-4-(4-methylpentyl)benzene 2-14ad



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate (**2-12a**) and 2-bromo-4-methylpentane (**2-13p**).

The ratio between the regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 85:15) gave 156 mg (81%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

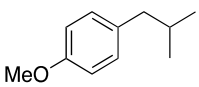


Peak Report 192

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	10.095	9.995	10.350	41566	2.08	8415	3.57	4.94	MI	
2	11.138	11.015	11.335	171817	8.60	41303	17.50	4.16	MI	
3	11.405	11.345	14.005	1784348	89.32	186232	78.93	9.58	MI	
				1997731	100.00	235950	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.07 (m, 2H), 6.85 – 6.81 (m, 2H), 3.80 (s, 3H), 2.56 – 2.50 (m, 2H), 1.63 – 1.52 (m, 3H), 1.26 – 1.18 (m, 2H), 0.88 (d, *J* = 6.6 Hz, 6H). The spectral data are consistent with those reported in the literature.[122]

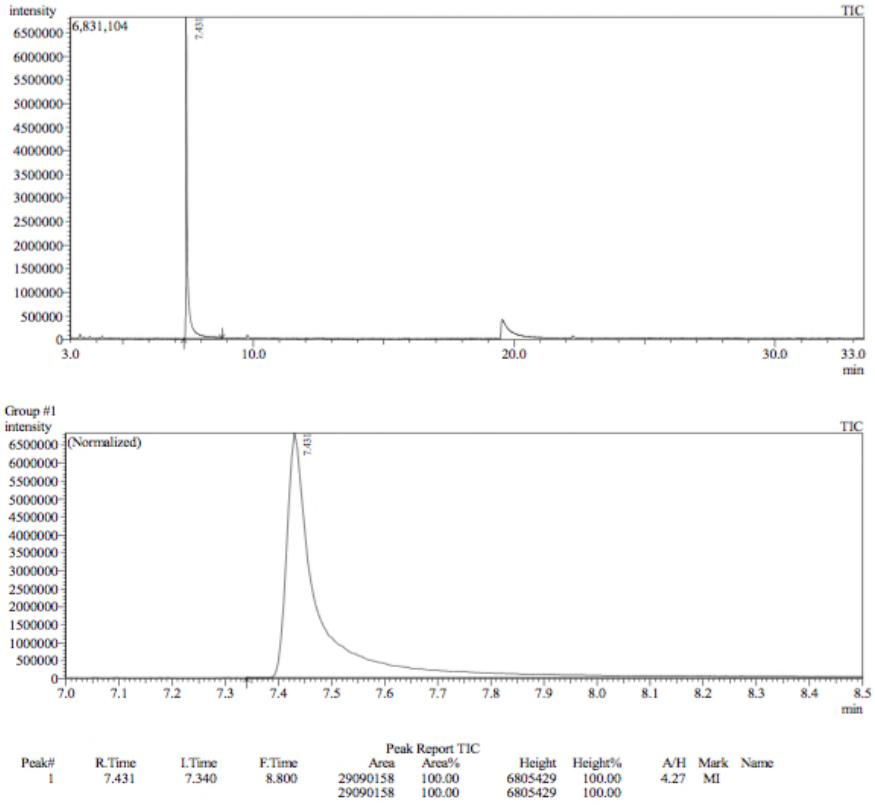
1-Isobutyl-4-methoxybenzene 2-14ae



In an argon-filled glove box, a Pyrex glass tube with a stirring bar was charged with LiCl (84.8 mg, 2 mmol, 2 equiv.), $ZnCl_2$ (273 mg, 2 mmol, 2 equiv.), Pd_2dba_3 (23 mg, 0.025 mmol, 2.5 mol%) and phosphine **L^6** (14.4 mg, 0.050 mmol, 5.0 mol%). The tube was sealed with a septum and paraffin, and was taken out. Under an argon atmosphere, THF (0.5 mL), *tert*-butylmagnesium chloride (2.0 mL, 2 mmol, 2 equiv., 1.0 M in THF) and

4-methoxyphenyl trifluoromethanesulfonate (**2-12a**, 256 mg, 1 mmol) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 48 h in an aluminum block. After this time, a fraction of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was measured by GCMS (linear/branched >99:1). Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered and concentrated. The residue was subjected to column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 85:15) to yield the product (104 mg, 63%).

GCMS chromatogram of the crude mixture

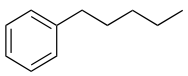


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	7.431	7.340	8.800	29090158	100.00	6805429	100.00	4.27	MI	
				29090158	100.00	6805429	100.00			

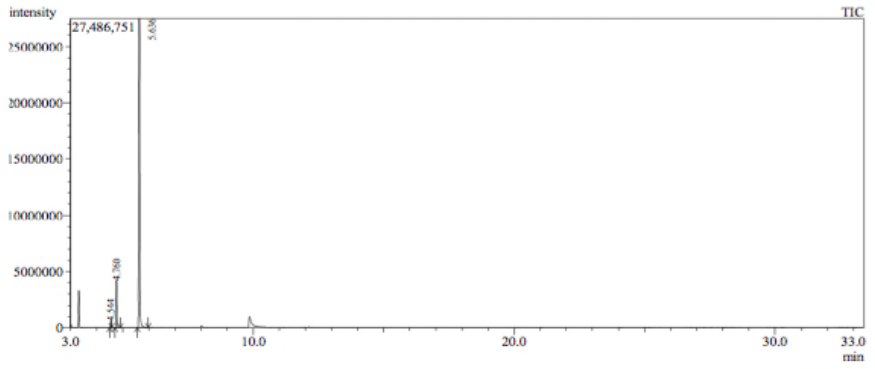
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 – 7.05 (m, 2H), 6.87 – 6.81 (m, 2H), 3.80 (s, 3H), 2.43 (d, *J* = 7.2 Hz, 2H), 1.91 – 1.77 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 6H). The spectral data is consistent with that reported in the literature.[125]

Pentylbenzene 2-14b



The above compound was synthesized according to the general procedure from phenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on silica gel (elution with pentane) gave 130 mg (88%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

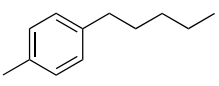


Peak Report148

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.544	4.505	4.585	90437	1.22	52763	1.49	1.71	MI	
2	4.761	4.715	4.840	698839	9.39	381904	10.81	1.83	MI	
3	5.636	5.545	6.000	6652824	89.39	3099809	87.70	2.15	MI	
				7442100	100.00	3534476	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 – 7.26 (m, 2H), 7.22 – 7.15 (m, 3H), 2.61 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.40 – 1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). The spectral data is consistent with that reported in the literature.[126]

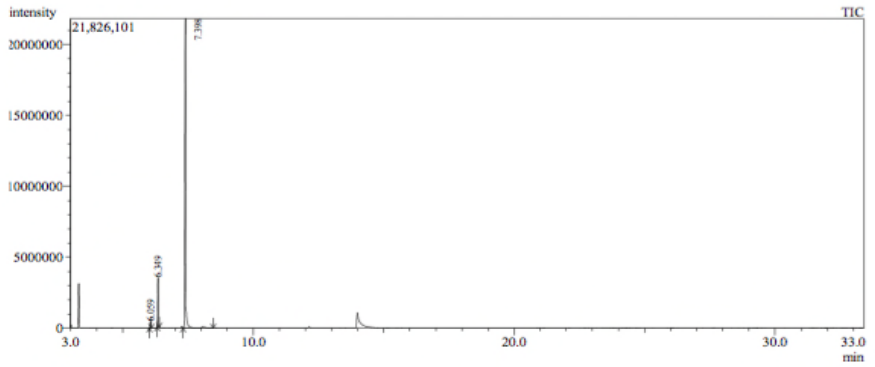
1-Methyl-4-pentylbenzene 2-14c

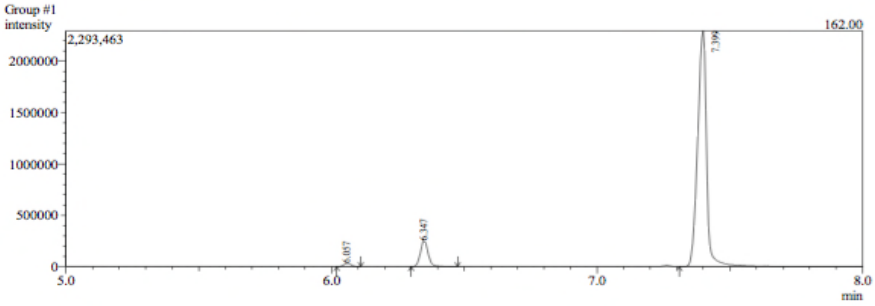


The above compound was synthesized according to the general procedure from 4-tolyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on

silica gel (elution from pentane to pentane/Et_2O 95:5) gave 102 mg (63%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



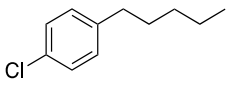


Peak Report 162

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	6.057	6.020	6.110	65739	1.10	33865	1.31	1.94	MI	
2	6.347	6.300	6.475	512599	8.59	252631	9.80	2.03	MI	
3	7.399	7.310	8.090	5390258	90.31	2292265	88.89	2.35	MI	
				5968596	100.00	2578761	100.00			

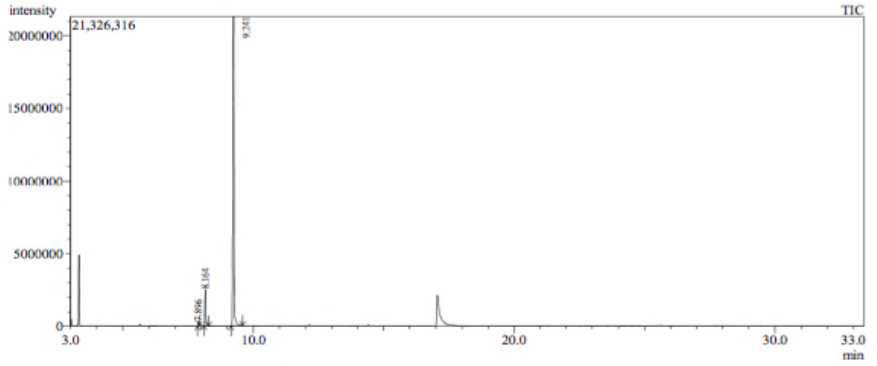
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 – 7.06 (m, 4H), 2.57 (t, *J* = 7.7 Hz, 2H), 2.33 (s, 3H), 1.66 – 1.56 (m, 2H), 1.39 – 1.29 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). The spectral data is consistent with that reported in the literature.[126]

1-Chloro-4-pentylbenzene 2-14d



The above compound was synthesized according to the general procedure from 4-chlorophenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on silica gel (elution with pentane) gave 132 mg (72%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	7.896	7.860	7.940	640688	1.06	327258	1.36	1.96	MI	
2	8.164	8.115	8.295	5498548	9.06	2489402	10.32	2.21	MI	
3	9.241	9.150	9.590	54569350	89.89	21297957	88.32	2.56	MI	
				60708586	100.00	24114617	100.00			

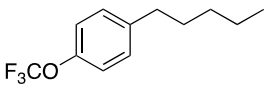
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.21 (m, 2H), 7.13 – 7.08 (m, 2H), 2.57 (t, *J* = 7.8 Hz, 2H), 1.64 – 1.55 (m, 2H), 1.36 – 1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 131.4, 129.9, 128.4, 35.4, 31.5, 31.2, 22.7, 14.2;

IR (neat) ν (cm^{-1}): 3060, 3025, 2953, 2923, 2854, 1492, 1451, 742, 698;

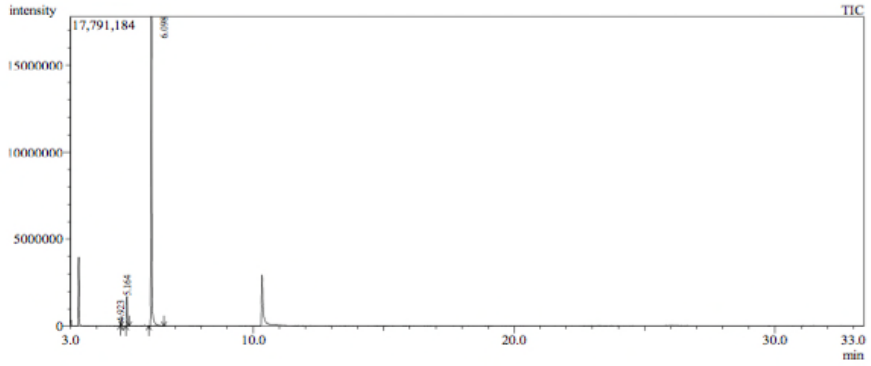
GCMS (EI) m/z for $C_{11}H_{15}Cl$ ($[M]^{+\bullet}$): 182.

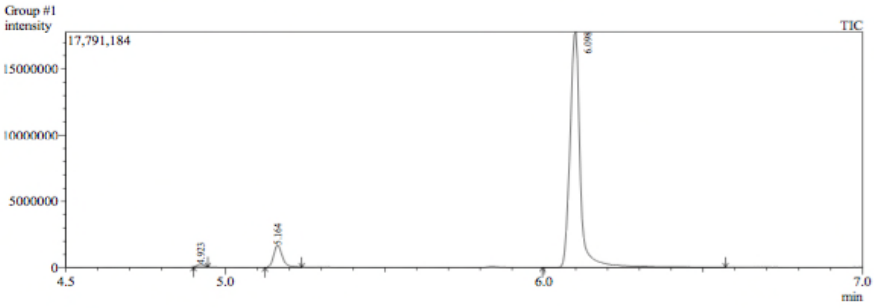
1-Pentyl-4-(trifluoromethoxy)benzene 2-14e



The above compound was synthesized according to the general procedure from 4-(trifluoromethoxy)phenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 92:8). Purification by column chromatography on silica gel (elution with pentane) gave 143 mg (62%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.923	4.900	4.945	341572	0.79	217415	1.10	1.57	MI	
2	5.164	5.125	5.240	3171424	7.34	1694908	8.61	1.87	MI	
3	6.098	5.995	6.570	39670574	91.86	17765066	90.28	2.23	MI	
				43183570	100.00	19677389	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.16 (m, 2H), 7.15 – 7.07 (m, 2H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.38 – 1.27 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H);

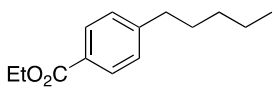
^{19}F NMR (376 MHz, $CDCl_3$) δ -57.94;

^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 141.8, 129.7, 120.9, 35.4, 31.6, 31.3, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 2930, 1508, 1256, 1221, 1163, 1245;

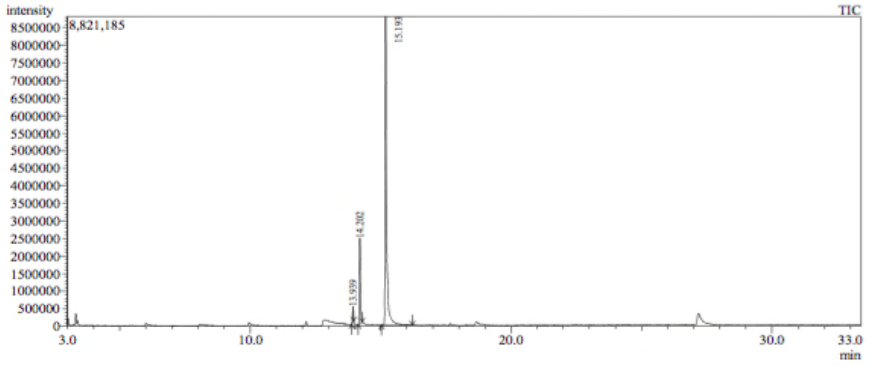
GCMS (EI) m/z for $C_{12}H_{15}F_3O$ ($[M]^{+\bullet}$): 232.

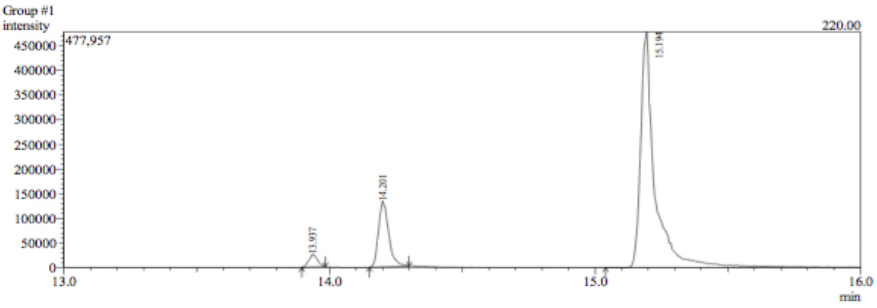
<u>Ethyl-4-pentylbenzoate 2-14f</u>



The above compound was synthesized according to the general procedure from ethyl 4-(trifluoromethylsulfonyloxy)benzoate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 82:18). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 70:30) gave 197 mg (89%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	13.939	13.890	13.970	994973	2.42	457479	3.92	2.17	MI	
2	14.202	14.140	14.295	6579554	16.03	2439740	20.89	2.70	MI	
3	15.193	15.025	16.215	33475403	81.55	8783492	75.20	3.81	MI	
				41049930	100.00	11680711	100.00			

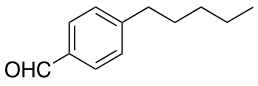
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.94 (m, 2H), 7.25 – 7.22 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 1.68 – 1.60 (m, 2H), 1.39 (t, *J* = 6.3 Hz, 3H), 1.36 – 1.28 (m, 4H), 0.89 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 148.5, 129.7, 128.5, 128.1, 60.9, 36.1, 31.6, 31.0, 22.6, 14.5, 14.1;

IR (neat): ν (cm^{-1}) 2929, 1715, 1270, 1103, 1021, 762;

HRMS (ESI): Calcd for $C_{14}H_{20}NaO_2$ ($[M+Na]^+$): 243.1361, found 243.1356.

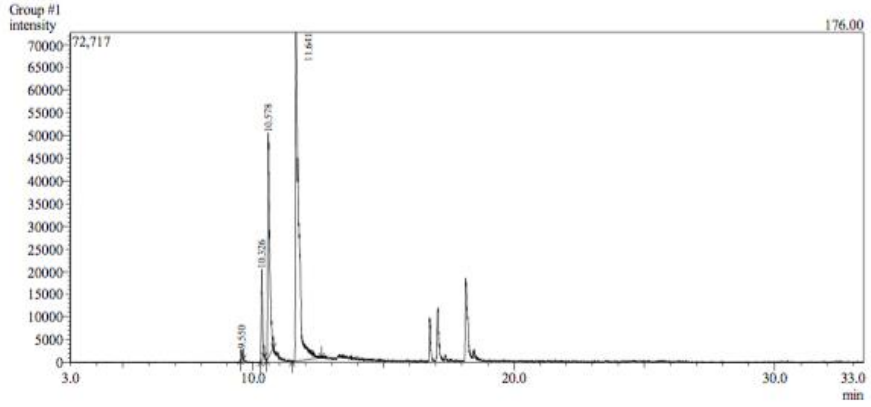
<u>4-Pentylbenzaldehyde 2-14g</u>

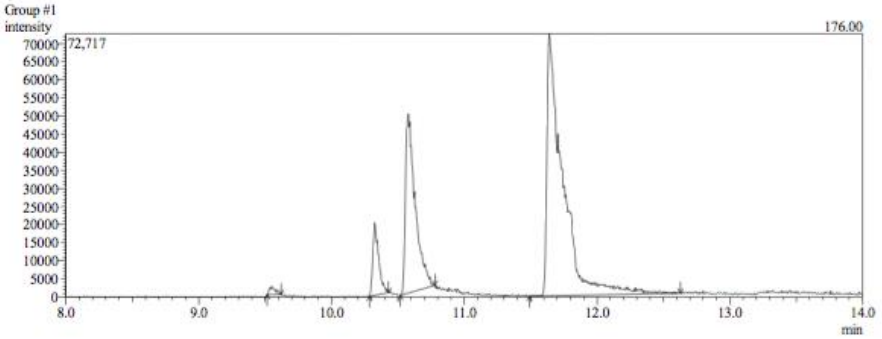


The above compound was synthesized according to the general procedure from 4-(formylphenyl) trifluoromethanesulfonate and 3-bromopentane (4 equiv.), Mg powder (4 equiv.), $ZnCl_2$ (4 equiv.) and LiCl (4 equiv.). The ratio between the regioisomers was determined by GCMS (linear/branched 65:35). Purification by column chromatography on

silica gel (elution from pentane to pentane/CH_2Cl 50:50) gave 97 mg (55%) of the mixture of regioisomers as yellow oil.

GCMS chromatogram of the crude mixture



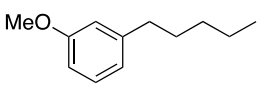


Peak Report 176

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	9.550	9.515	9.620	6605	0.72	2313	1.60	2.86	MI	
2	10.326	10.285	10.430	60266	6.54	20127	13.94	2.99	MI	
3	10.578	10.520	10.780	253870	27.54	49538	34.31	5.12	MI	
4	11.641	11.490	12.630	601024	65.20	72409	50.15	8.30	MI	
				921765	100.00	144387	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.83 – 7.77 (m, 2H), 7.36 – 7.32 (m, 2H), 2.68 (t, *J* = 7.3 Hz, 2H), 1.69 – 1.62 (m, 2H), 1.37 – 1.29 (m, 4H), 0.90 (t, *J* = 6.7 Hz, 3H). The spectral data is consistent with that reported in the literature.[127]

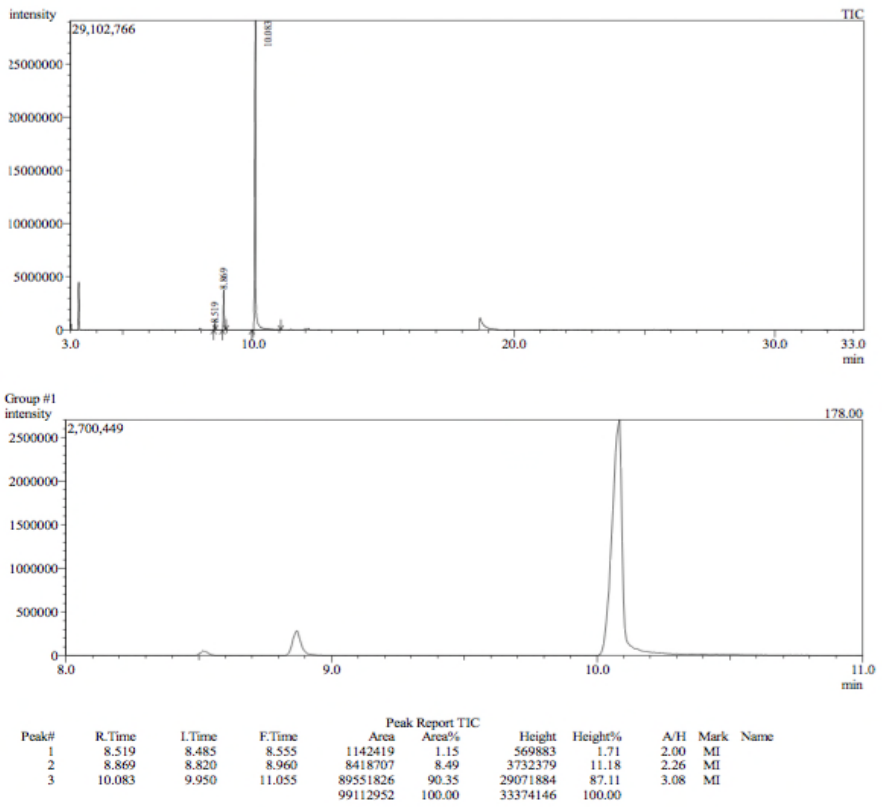
1-Methoxy-3-pentylbenzene 2-14h



The above compound was synthesized according to the general procedure from 3-methoxyphenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column

chromatography on silica gel (elution with pentane) gave 156 mg (89%) of the mixture of regioisomers as pale yellow oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	8.519	8.485	8.555	1142419	1.15	569883	1.71	2.00	MI	
2	8.869	8.820	8.960	8418707	8.49	3732379	11.18	2.26	MI	
3	10.083	9.950	11.055	89551826	90.35	29071884	87.11	3.08	MI	
				99112952	100.00	33374146	100.00			

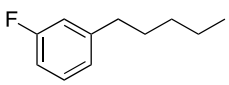
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (td, *J* = 7.4, 1.4 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.75 – 6.71 (m, 2H), 3.81 (s, 3H), 2.58 (t, *J* = 7.4 Hz, 2H), 1.68 – 1.55 (m, 2H), 1.40 – 1.28 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 144.8, 129.3, 121.0, 114.3, 110.9, 55.3, 36.1, 31.7, 31.2, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 2927, 2856, 1584, 1454, 1259, 1152, 1047;

GCMS (EI) m/z for $C_{12}H_{18}O$ ($[M]^{+\bullet}$): 178.

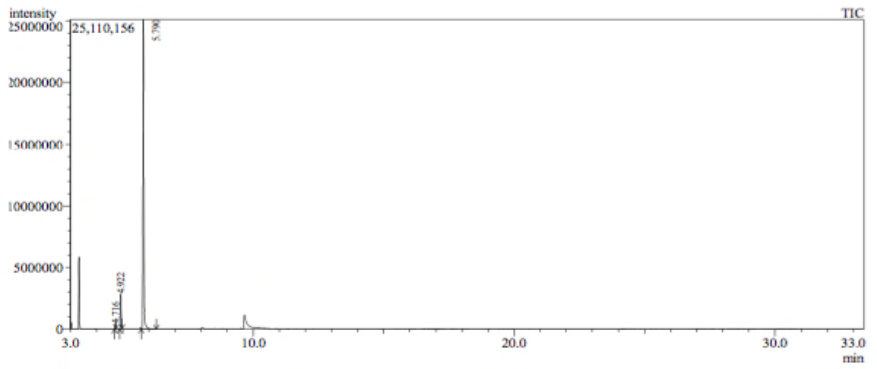
<u>1-Fluoro-3-pentylbenzene 2-14i</u>

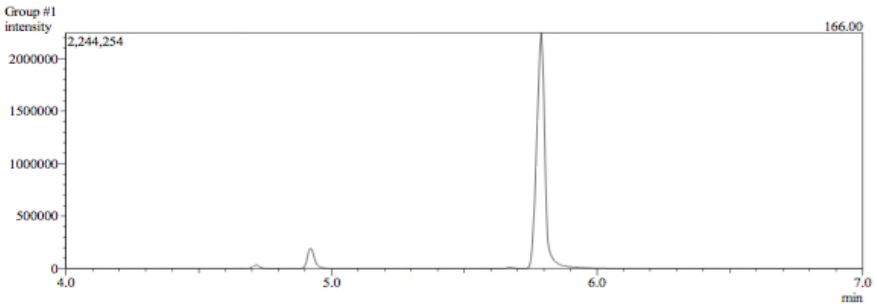


The above compound was synthesized according to the general procedure from 3-fluorophenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the

regioisomers was determined by GCMS (linear/branched 91:9). Purification by column chromatography on silica gel (elution with pentane) gave 118 mg (71%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.716	4.685	4.750	719461	1.13	424846	1.50	1.69	MI	
2	4.922	4.880	4.985	5240532	8.21	2826214	9.98	1.85	MI	
3	5.790	5.710	6.285	57862582	90.66	25077503	88.52	2.31	MI	
				63822575	100.00	28328563	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 – 7.19 (m, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.91 – 6.84 (m, 2H), 2.60 (t, *J* = 7.8 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.38 – 1.27 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H);

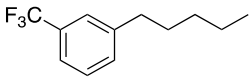
^{19}F NMR (376 MHz, $CDCl_3$) δ -114.19;

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.0 (d, *J* = 244.9 Hz), 145.7 (d, *J* = 7.0 Hz), 129.7 (d, *J* = 8.4 Hz), 124.2 (d, *J* = 2.6 Hz), 115.3 (d, *J* = 20.6 Hz), 112.5 (d, *J* = 21.1 Hz), 35.8, 31.6, 31.0, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 2927, 2858, 1590, 1488, 1448, 1253, 1140, 781;

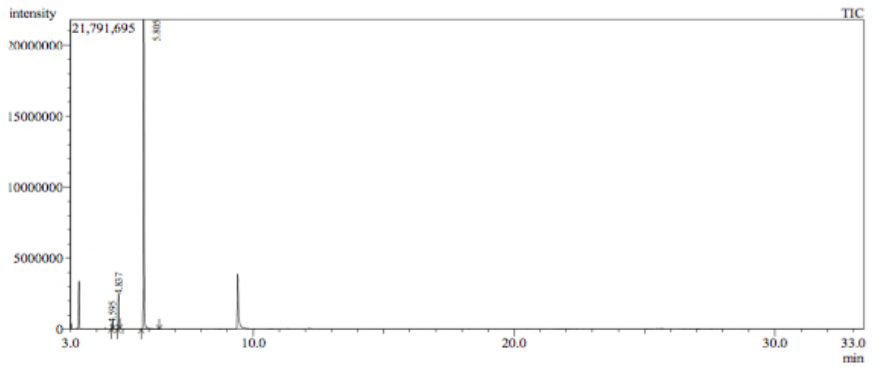
GCMS (EI) m/z for $C_{11}H_{15}F$ ($[M]^{+\bullet}$): 166.

<u>1-Pentyl-3-(trifluoromethyl)benzene 2-14j</u>



The above compound was synthesized according to the general procedure from 3-(trifluoromethyl)phenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on silica gel (elution with pentane) gave 158 mg (73%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.595	4.565	4.625	631317	1.31	406653	1.65	1.55	MI	
2	4.837	4.800	4.885	4218672	8.73	2415504	9.82	1.75	MI	
3	5.805	5.710	6.395	43482206	89.97	21767056	88.52	2.00	MI	
				48332195	100.00	24589213	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.40 – 7.33 (m, 2H), 2.66 (t, *J* = 7.1 Hz, 2H), 1.68 – 1.59 (m, 2H), 1.38 – 1.30 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H);

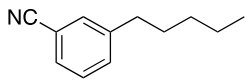
^{19}F NMR (376 MHz, $CDCl_3$) δ -62.54;

^{13}C NMR (100 MHz, $CDCl_3$) δ 143.9, 131.9, 130.7 (q, *J* = 32.0 Hz), 128.7, 125.2 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 273.2 Hz), 122.6 (q, *J* = 3.8 Hz), 35.9, 31.6, 31.1, 22.6, 14.1;

IR (neat): ν (cm^{-1}) 2958, 2928, 2858, 1325, 1162, 1123, 1073, 798, 702, 661;

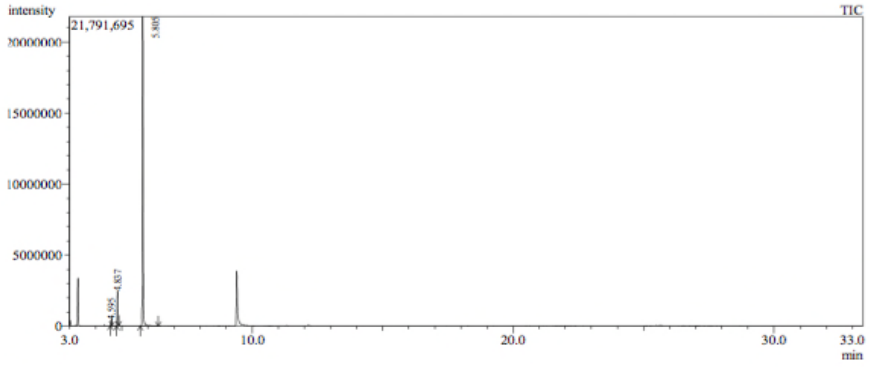
GCMS (EI) m/z for $C_{12}H_{15}F_3$ ($[M]^{+\bullet}$): 216.

3-Pentylbenzonitrile 2-14k



The above compound was synthesized according to the general procedure from 3-cyanophenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 80:20) gave 150 mg (87%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture

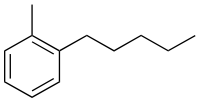


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.595	4.565	4.625	631317	1.31	406653	1.65	1.55	MI	
2	4.837	4.800	4.885	4218672	8.73	2415504	9.82	1.75	MI	
3	5.805	5.710	6.395	43482206	89.97	21767056	88.52	2.00	MI	
				48332195	100.00	24589213	100.00			

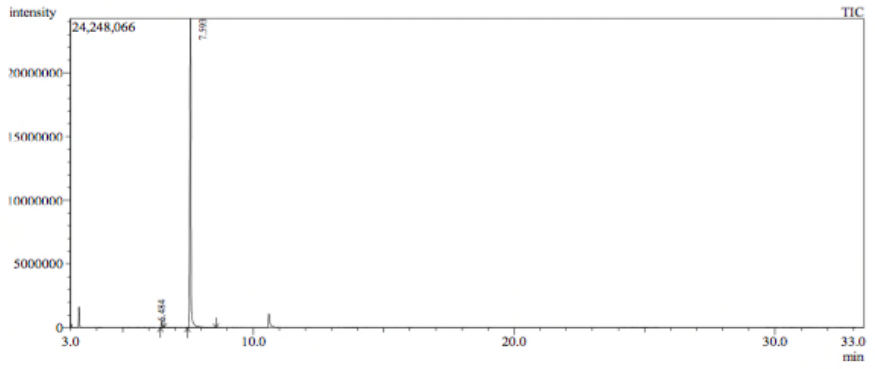
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 – 7.44 (m, 2H), 7.43 – 7.34 (m, 2H), 2.63 (t, *J* = 7.3 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.38 – 1.29 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H). The spectral data is consistent with that reported in the literature.[128]

1-Methyl-2-pentylbenzene 2-14l



The above compound was synthesized according to the general procedure from 2-tolyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 98:2). Purification by column chromatography on silica gel (elution using pentane) gave 144 mg (89%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	6.484	6.440	6.570	1113492	1.64	495137	2.00	2.25	MI	
2	7.593	7.480	8.565	66916493	98.36	24231149	98.00	2.76	MI	
				68029985	100.00	24726286	100.00			

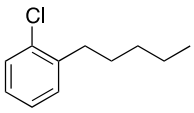
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.07 (m, 4H), 2.59 (t, *J* = 7.7 Hz, 2H), 2.31 (s, 3H), 1.63 – 1.55 (m, 2H), 1.41 – 1.33 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.0, 130.2, 128.9, 126.0, 125.8, 33.5, 32.1, 30.1, 22.8, 19.4, 14.2;

IR (neat): ν (cm^{-1}) 2926, 2858, 1492, 1459, 739;

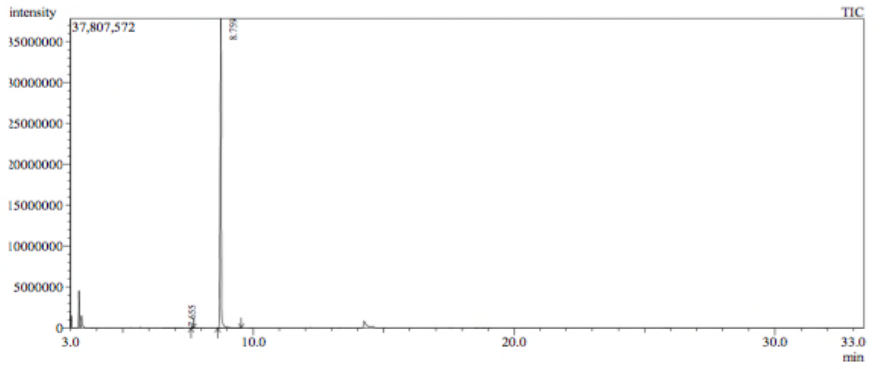
GCMS (EI) m/z for $C_{12}H_{18}$ ($[M]^{+\bullet}$): 162.

<u>1-Chloro-2-pentylbenzene 2-14m</u>



The above compound was synthesized according to the general procedure from 2-chlorophenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 99.5:0.5). Purification by column chromatography on silica gel (elution using pentane) gave 121 mg (66%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	7.655	7.620	7.715	484322	0.46	205689	0.54	2.35	MI	
2	8.759	8.635	9.535	104746394	99.54	37769225	99.46	2.77	MI	
				105230716	100.00	37974914	100.00			

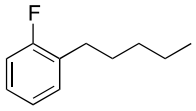
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.23 – 7.09 (m, 3H), 2.72 (t, *J* = 7.6 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.40 – 1.32 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 134.0, 130.5, 129.5, 127.2, 126.8, 33.7, 31.8, 29.6, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 2926, 2858, 1473, 1442, 1051, 1033, 749;

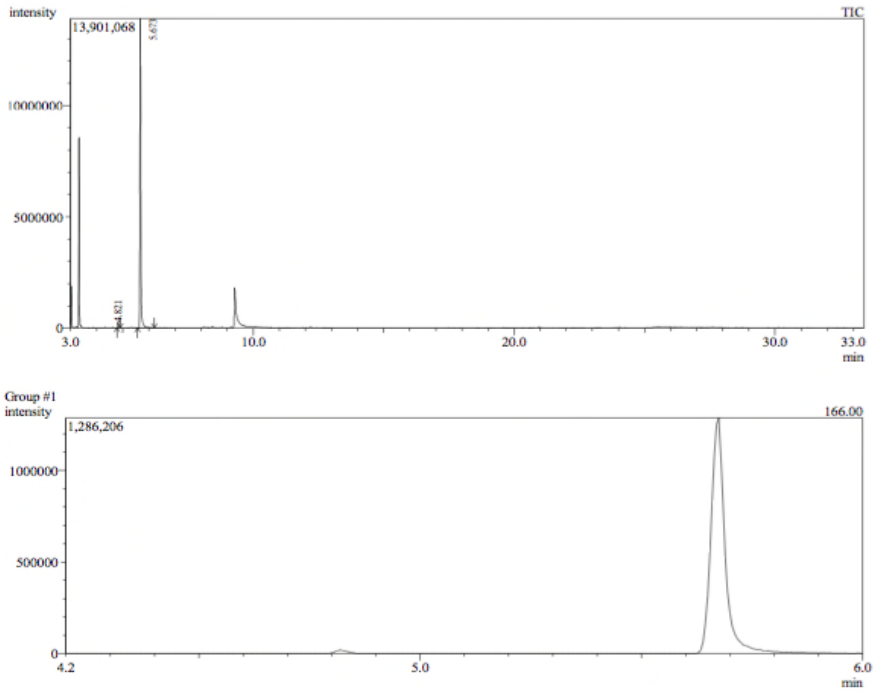
GCMS (EI) m/z for $C_{11}H_{15}Cl$ ($[M]^{+\bullet}$): 182.

1-Fluoro-2-pentylbenzene 2-14n



The above compound was synthesized according to the general procedure from 2-fluorophenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 98:2). Purification by column chromatography on silica gel (elution using pentane) gave 101 mg (61%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.821	4.780	4.905	537293	1.66	261516	1.85	2.05	MI	
2	5.673	5.570	6.215	31879634	98.34	13873663	98.15	2.30	MI	
				32416927	100.00	14135179	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.12 (m, 2H), 7.05 (td, *J* = 7.4, 1.3 Hz, 1H), 7.00 (ddd, *J* = 9.4, 8.0, 1.2 Hz, 1H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.57 (m, 2H), 1.39 – 1.31 (m, 4H), 0.90 (t, *J* = 6.6 Hz, 3H);

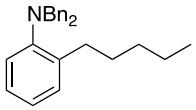
^{19}F NMR (376 MHz, $CDCl_3$) δ -119.11;

^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (d, *J* = 244.3 Hz), 130.7 (d, *J* = 5.3 Hz), 129.8 (d, *J* = 16.1 Hz), 127.4 (d, *J* = 8.1 Hz), 123.9 (d, *J* = 3.5 Hz), 115.2 (d, *J* = 22.4 Hz), 31.7, 30.0, 29.1 (d, *J* = 2.3 Hz), 22.6, 14.2;

IR (neat): ν (cm^{-1}) 2923, 2854, 1491, 1457, 1229, 1120, 753;

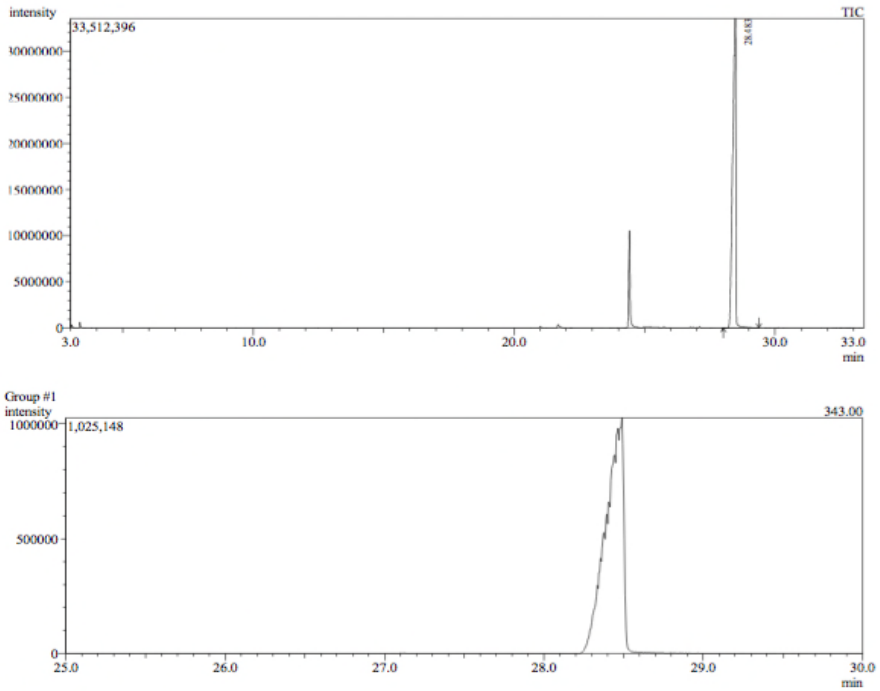
GCMS (EI) m/z for $C_{11}H_{15}F$ ($[M]^{+\bullet}$): 166.

<u>*N*,*N*-Dibenzyl-2-pentylaniline 2-14o</u>



The above compound was synthesized according to the general procedure from 2-(dibenzylamino)phenyl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched >99/1). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 92:8) gave 283 mg (82%) colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	28.483	28.025	29.385	282351896	100.00	33460051	100.00	8.44	MI	
				282351896	100.00	33460051	100.00			

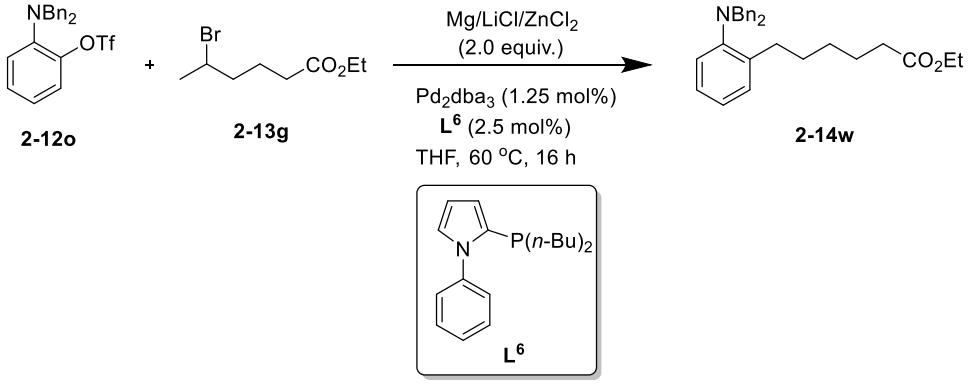
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 – 7.18 (m, 11H), 7.10 – 6.99 (m, 3H), 4.05 (s, 4H), 2.80 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.56 (m, 2H), 1.43 – 1.33 (m, 4H), 0.92 (t, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 139.2, 138.7, 129.7, 129.0, 128.2, 127.0, 126.0, 124.1, 123.3, 58.0, 32.4, 30.7, 30.6, 22.8, 14.3;

IR (neat): ν (cm^{-1}) 3060, 3025, 2953, 2923, 2854, 1492, 1451, 742, 698;

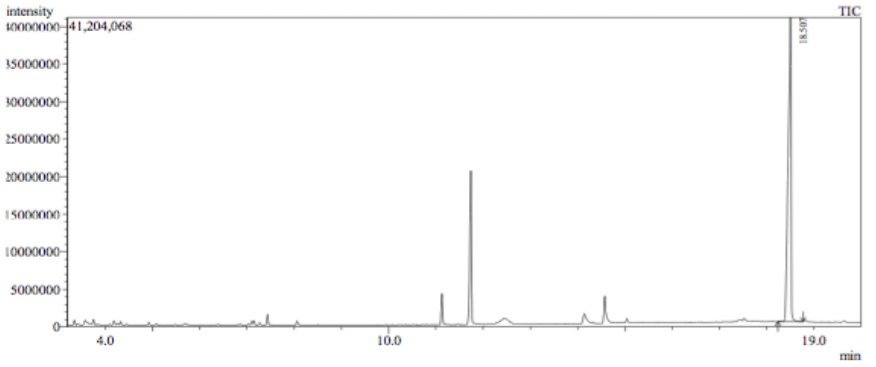
HRMS (ESI): Calcd for $C_{25}H_{30}N$ ($[M+H]^+$): 344,2378, found 344.2377.

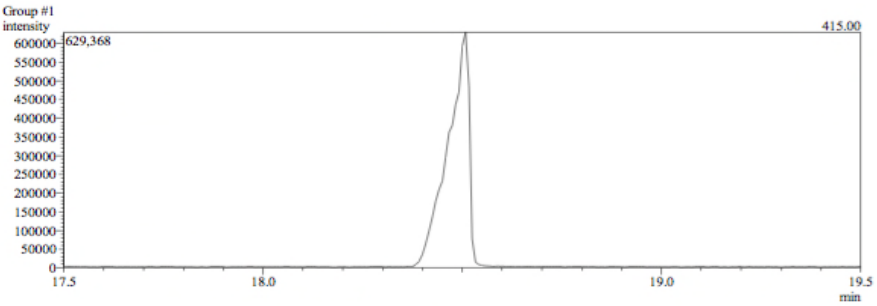
6-(2-Aminophenyl)hexanoic acid 2-16



The above compound was synthesized according to the general procedure from 2-(dibenzylamino)phenyl trifluoromethanesulfonate (**2-12o**) and ethyl 5-bromohexanoate (**2-13g**). The ratio between the regioisomers was determined by GCMS (linear/branched >99/1). The reaction mixture was quenched with NH_4Cl (3 mL) and extracted twice with Et_2O (2 x 10 mL). The organic layers were dried over $MgSO_4$, filtered off and concentrated to dryness. The residue was directly used in the next step.

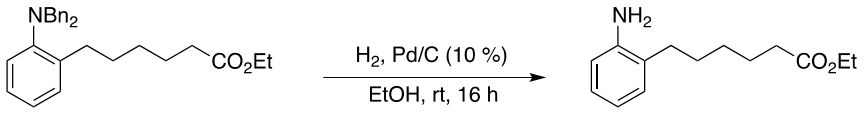
GCMS chromatogram of the crude mixture



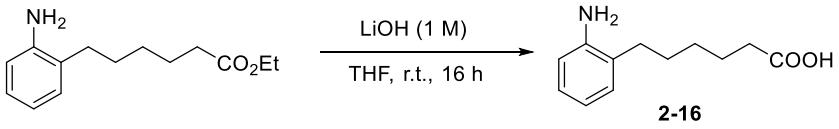


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	18.507	18.242	18.775	170422267	100.00	40494343	100.00	4.21	MI	
				170422267	100.00	40494343	100.00			



The crude residue was dissolved in EtOH (10 mL) and Pd/C (10 %) was added in one portion. The atmosphere was replaced by hydrogen (1 atm.) by three cycle of vacuum / H_2. After overnight, the resulting mixture was filtered through a pad of celite and rinced with CH_2Cl_2 (20 mL). The filtrate was concentrated in vacuo and purified by column chromatography (elution from CH_2Cl_2 to CH_2Cl_2/MeOH 97:3) to give 130 mg of ethyl 6-(2-aminophenyl)hexanoate (55% for two steps) as an oil.



2-16

To a solution of LiOH (1M) was added ethyl 6-(2-aminophenyl)hexanoate (120 mg, 0.51 mmol) in THF (5 mL). The reaction mixture was stirred at room temperature for 16 h. After completion, the crude mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (15 mL). The aqueous phase was acidified to pH = 6 and extracted twice with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered off

and concentrated in vacuo to furnish the desired product **2-16** as a white solid (107 mg, quant.).

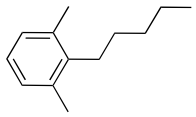
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 – 7.01 (m, 2H), 6.74 (td, *J* = 7.4, 1.2 Hz, 1H), 6.68 (dd, *J* = 8.2, 1.2 Hz, 1H), 2.50 (t, *J* = 7.8 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.74 – 1.62 (m, 4H), 1.49 – 1.42 (m, 2H);

^{13}C NMR (126 MHz, $CDCl_3$) δ 179.2, 144.0, 129.6, 127.1, 126.7, 119.0, 115.8, 34.0, 31.2, 29.2, 28.5, 24.7;

IR (neat): ν (cm^{-1}) 3388, 3322, 2933, 2903, 2859, 1716, 1621, 1455, 1492, 1229, 1176, 962, 792, 767, 732, 671, 443;

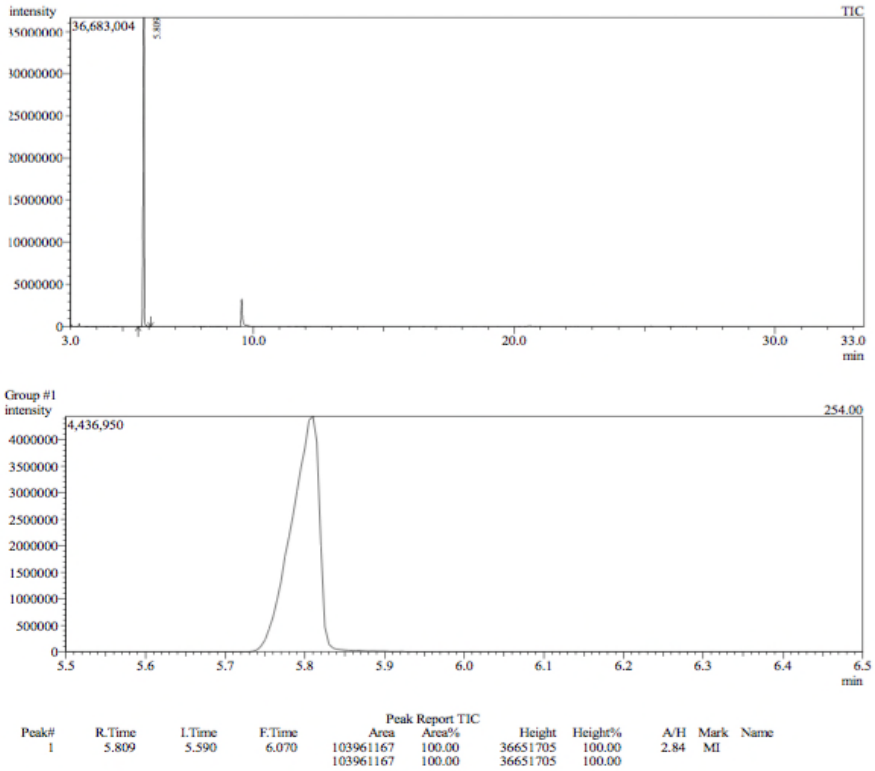
HRMS (ESI): Calcd for $C_{12}H_{18}NO_2$ ($[M+H]^+$): 208.1338, found 208.1334.

1,3-Dimethyl-2-pentylbenzene 2-14p



The above compound was synthesized according to the general procedure from 2,6-dimethylphenyl trifluoromethanesulfonate and 3-bromopentane using Pd_2dba_3 (2.5 mol%) and phosphine **L^{6}** (5 mol%). The ratio between the regioisomers was determined by GCMS (linear/branched >99/1). Purification by column chromatography on silica gel (elution using pentane) gave 72 mg (41%) of **2-14p** as colourless oil.

GCMS chromatogram of the crude mixture



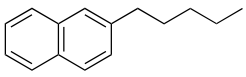
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (s, 3H), 2.67 – 2.51 (m, 2H), 2.32 (s, 6H), 1.52 – 1.35 (m, 6H), 0.92 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 136.1, 128.2, 125.5, 32.6, 29.9, 29.9, 28.9, 22.7, 19.9, 14.2;

IR (neat): ν (cm^{-1}) 2953, 2922, 2854, 1465, 1377, 765;

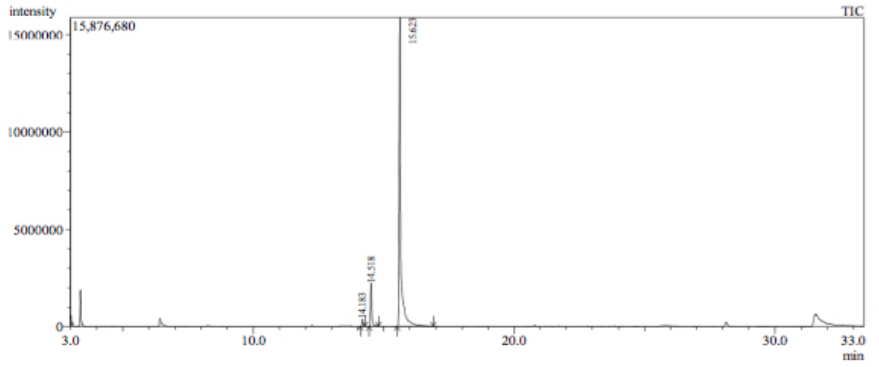
GCMS (EI) m/z for $C_{13}H_{20}$ ($[M]^{+\bullet}$): 176.

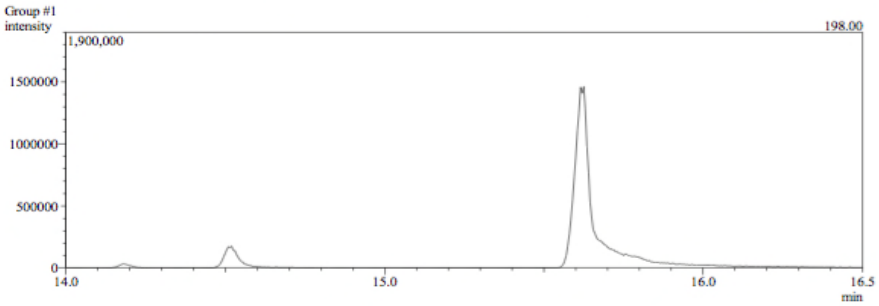
2-Pentylnaphthalene 2-14q



The above compound was synthesized according to the general procedure from (naphthalen-2-yl trifluoromethanesulfonate) and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on silica gel (elution using pentane) gave 170 mg (86%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	14.183	14.110	14.280	1025647	1.36	375654	2.04	2.73	MI	
2	14.518	14.440	14.805	7225746	9.56	2227197	12.07	3.24	MI	
3	15.623	15.510	16.900	67303712	89.08	15846738	85.89	4.25	MI	
				75555105	100.00	18449589	100.00			

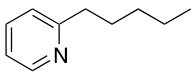
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.75 (m, 3H), 7.63 – 7.60 (m, 1H), 7.48 – 7.39 (m, 2H), 7.38 – 7.32 (m, 1H), 2.78 (t, *J* = 7.5 Hz, 2H), 1.77 – 1.66 (m, 2H), 1.41 – 1.33 (m, 4H), 0.91 (t, *J* = 6.7 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 133.8, 132.1 127.8, 127.7, 127.6, 127.5, 126.4, 125.9, 125.1, 36.3, 31.7, 31.2, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 3050, 2957, 2925, 2854, 1600, 1508, 1457, 1377, 853, 815, 744, 476;

GCMS (EI) m/z for $C_{15}H_{18}$ ($[M]^{+\bullet}$): 198.

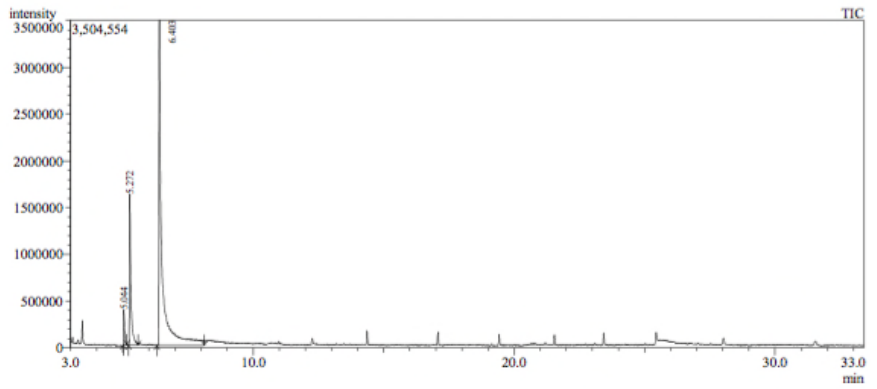
2-Pentylpyridine 2-14r

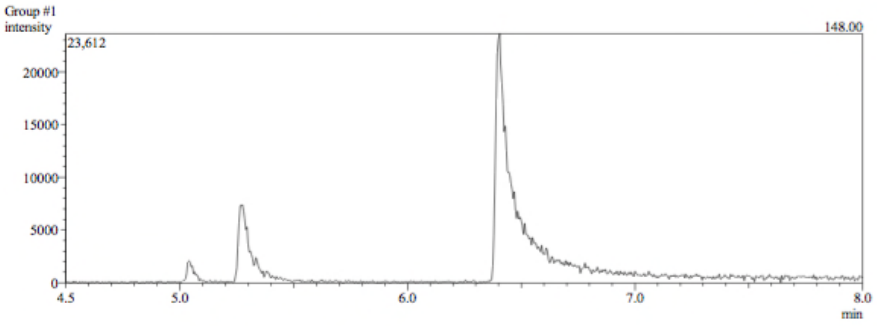


The above compound was synthesized according to the general procedure from pyridin-2-yl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 79:21). Purification by column chromatography on silica gel (elution from pentane/EtOAc 90:10 to 60:40) gave 132 mg (88%) of the mixture of regioisomers as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 – 8.48 (m, 1H), 7.58 (tt, *J* = 7.6, 1.9 Hz, 1H), 7.13 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.08 (ddd, *J* = 7.5, 4.9, 1.2 Hz, 1H), 2.77 (t, *J* = 7.5 Hz, 2H), 1.78 – 1.68 (m, 2H), 1.39 – 1.31 (m, 4H), 0.89 (t, *J* = 7.2 Hz, 3H). The spectral data is consistent with that reported in the literature.[129]

GCMS chromatogram of the crude mixture

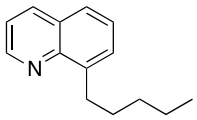




Peak Report TIC

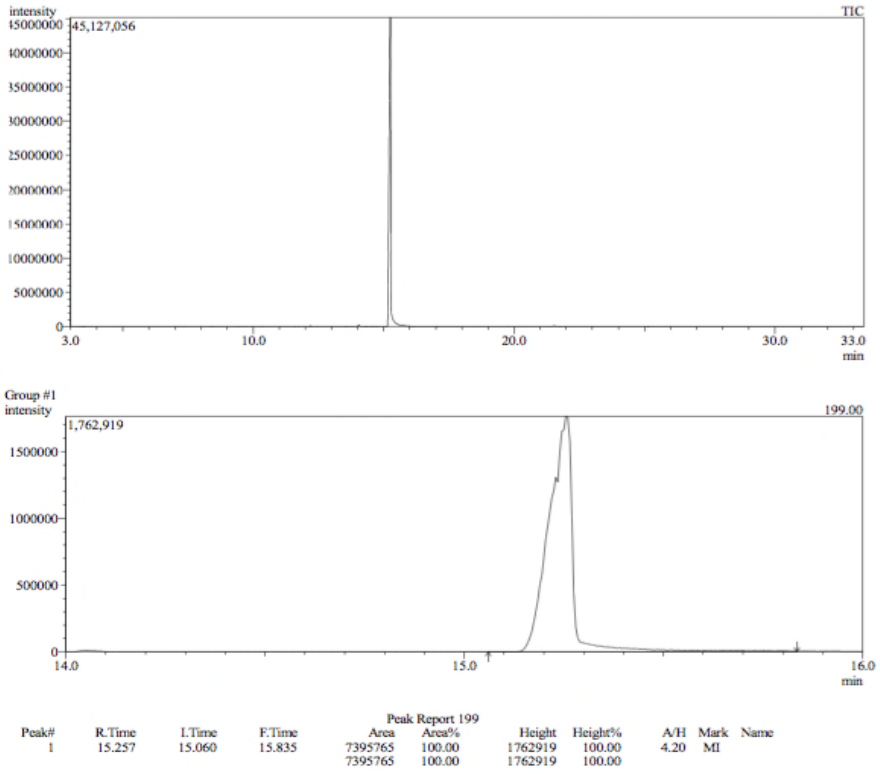
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	5.044	5.015	5.150	972149	2.97	378779	6.92	2.57	MI	
2	5.272	5.220	5.590	5853224	17.88	1618254	29.57	3.62	MI	
3	6.403	6.305	8.120	25903132	79.15	3475678	63.51	7.45	MI	
				32728505	100.00	5472711	100.00			

8-Pentylquinoline 2-14s



The above compound was synthesized according to the general procedure from quinolin-8-yl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers could not be determined by GCMS (overlapping of the two peaks). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 93:7) gave 102 mg (51%) of the pure compound **2-14s** as colourless oil.

GCMS chromatogram of the isolated product



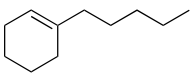
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.56 (ddt, *J* = 7.0, 1.5, 0.8 Hz, 1H), 7.46 (dd, *J* = 8.1, 7.1 Hz, 1H), 7.38 (dd, *J* = 8.2, 4.2 Hz, 1H), 3.28 (t, *J* = 7.6 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.48 – 1.34 (m, 4H), 0.90 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 147.1, 141.8, 136.5, 128.8, 128.6, 126.4, 125.9, 120.9, 32.1, 31.5, 30.5, 22.8, 14.2;

IR (neat): ν (cm^{-1}) 2953, 2923, 2855, 1498, 1466, 1366, 825, 794;

HRMS (ESI): Calcd for $C_{14}H_{18}N$ ($[M+H]^+$): 200.1439, found 200.1435;

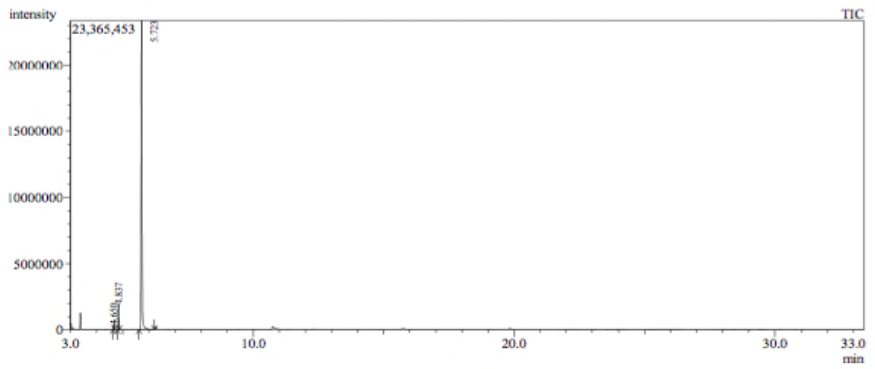
1-Penty-1-cyclohexene 2-14t



The above compound was synthesized according to the general procedure from cyclohex-1-en-1-yl trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 93:7). Purification by column

chromatography on silica gel (elution using pentane) gave 149 mg (98%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	4.650	4.625	4.685	571269	1.01	343827	1.34	1.66	MI	
2	4.837	4.795	4.870	3525710	6.23	1914355	7.48	1.84	MI	
3	5.723	5.625	6.210	52516882	92.76	23343666	91.18	2.25	MI	
				56613861	100.00	25601848	100.00			

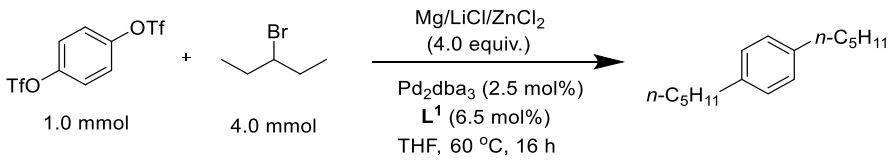
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.41 – 5.35 (m, 1H), 2.02 – 1.86 (m, 6H), 1.65 – 1.52 (m, 4H), 1.42 – 1.19 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 120.6, 38.2, 31.8, 28.5, 27.6, 25.4, 23.2, 22.8, 22.8, 14.3;

IR (neat): ν (cm^{-1}) 2922, 2856, 1458, 1438, 917;

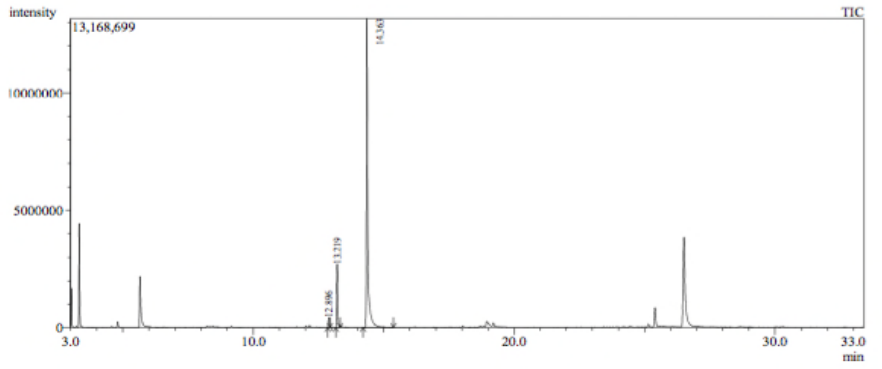
GCMS (EI) m/z for $C_{11}H_{20}$ ($[M]^{+\bullet}$): 152.

<u>1,4-Dipentylbenzene 2-14u</u>



The above compound was synthesized according to the general procedure from 1,4-benzenebis(trifluoromethanesulfonate) and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 85:15). Purification by column chromatography on silica gel (elution using pentane) gave 154 mg (71%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	12.896	12.855	12.945	998037	1.88	427333	2.63	2.34	MI	
2	13.219	13.160	13.330	6931634	13.06	2694200	16.56	2.57	MI	
3	14.363	14.210	15.370	45161798	85.06	13148839	80.81	3.43	MI	
				53091469	100.00	16270372	100.00			

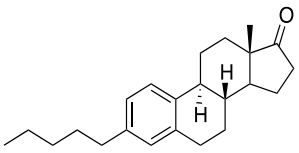
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4H), 2.57 (t, *J* = 7.5 Hz, 4H), 1.67 – 1.56 (m, 4H), 1.38 – 1.29 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 128.4, 35.7, 31.7, 31.4, 22.7, 14.2;

IR (neat): ν (cm^{-1}) 2956, 2924, 2855, 1513, 1458;

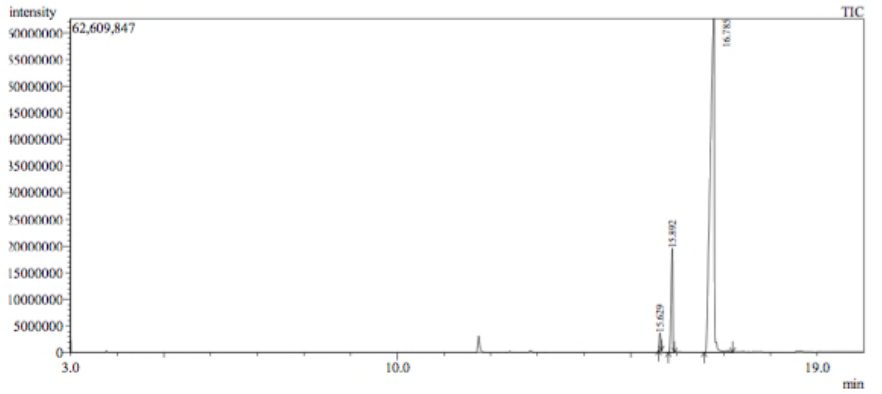
GCMS (EI) m/z for $C_{16}H_{26}$ ($[M]^{+\bullet}$): 218.

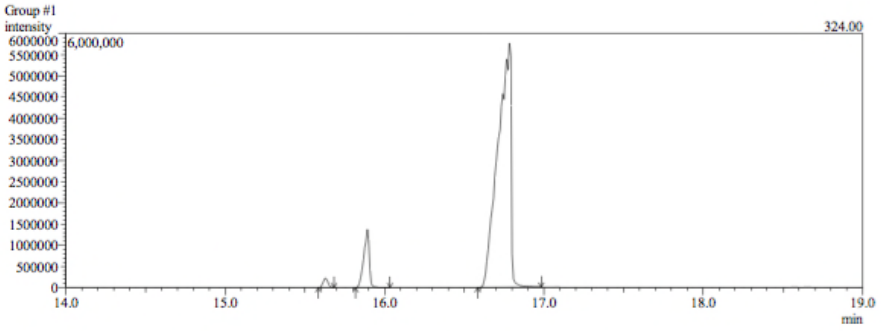
<u>1-Pentyl estra-1,3,5(10)-trien-17-one 2-14v</u>



The above compound was synthesized according to the general procedure from estrone trifluoromethanesulfonate and 3-bromopentane. The ratio between the regioisomers was determined by GCMS (linear/branched 90:10). Purification by column chromatography on silica gel (elution from pentane to pentane/Et_2O 70:30) gave 190 mg (59%) of the mixture of regioisomers as a white off solid.

GCMS chromatogram of the crude mixture





Peak Report 324

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	15.628	15.583	15.683	475275	1.28	219846	2.99	2.16	MI	
2	15.892	15.817	16.033	3319934	8.93	1374239	18.66	2.42	MI	
3	16.785	16.583	16.983	33367395	89.79	5770148	78.35	5.78	MI	
				37162604	100.00	7364233	100.00			

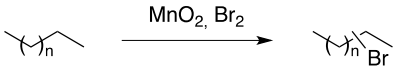
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.94 (s, 1H), 2.94 – 2.88 (m, 2H), 2.59 – 2.47 (m, 3H), 2.46 – 2.39 (m, 1H), 2.34 – 2.26 (m, 1H), 2.21 – 1.94 (m, 4H), 1.70 – 1.42 (m, 9H), 1.38 – 1.33 (m, 3H), 0.92 (t, *J* = 2.9 Hz, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 220.8, 140.4, 136.9, 136.2, 129.0, 125.9, 125.2, 50.6, 48.0, 44.4, 38.3, 35.9, 35.5, 31.7, 31.7, 31.3, 29.5, 26.7, 25.8, 22.6, 21.6, 14.1, 14.0;

IR (neat): ν (cm^{-1}) 2923, 2856, 1736, 1499, 1454, 1405, 1374, 1256, 1082, 1005, 820;

HRMS (ESI): Calcd for $C_{23}H_{32}NaO$ ($[M+Na]^+$): 347.2351, found 347.2342.

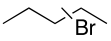
General procedure for the bromination of alkanes



The mixtures of alkyl bromides were prepared according to a literature procedure.[67]

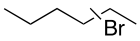
The alkane (50 or 100 mL), Br_2 (5 or 10 mmol) and MnO_2 (85%, 10 mmol or 20 mmol, 2 equiv.) were charged in a round-bottom flask and heated at the appropriate temperature until the disappearance of bromine color. After completion, the reaction mixture was filtered and the filtrate was washed with water. The combined organic phases were dried over $MgSO_4$. The residue was then distilled to afford the mixture of alkane isomer. The ratio between isomers was either determined by ^{1}H NMR or GCMS.

Bromopentane isomers



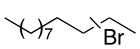
This mixture was prepared according to the general procedure from pentane (36 °C, 1 h) to furnish mixture in 47% yield (0.7 g) as colourless oil. The ratio between isomers was determined by ^{1}H NMR (2-bromopentane/3-bromopentane = 79:21) by comparison with commercially available compounds.

Bromohexane isomers



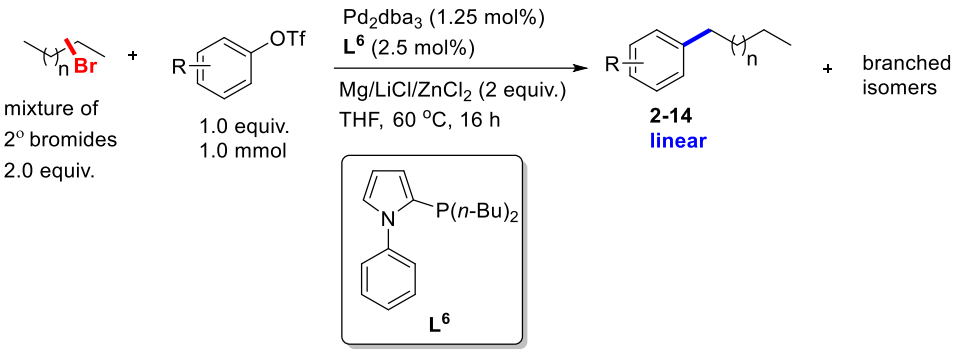
This mixture was prepared according to the general procedure from hexane (60 °C, 20 min) to furnish mixture in 45% yield (0.74 g) as brown oil. The ratio between isomers was determined by ^{1}H NMR (2-bromohexane/3-bromohexane = 59:41) by comparison with commercially available compounds.

Bromododecane isomers



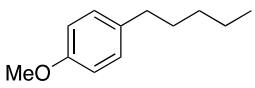
This mixture was prepared according to the general procedure (80 °C, 2 h) to furnish mixture in 79% yield (1.02 g) as yellow oil. The ratio between isomers was determined by GCMS (ratio of mixture of five secondary bromododecane isomers: 19:17:20:18:26)

General procedure for the cross-coupling reaction of aryl triflates and mixtures of alkyl bromides



In an argon-filled glove box, a Pyrex glass tube with stir bar was charged with LiCl (85 mg, 2 mmol, 2 equiv.), Mg (49 mg, 2 mmol, 2 equiv.), $ZnCl_2$ (273 mg, 2 mmol, 2 equiv.), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 1.25 mol%) and phosphine **L^6** (7.2 mg, 0.025 mmol, 2.5 mol%). The tube was sealed with a septum and paraffin, and was taken out. Under an argon atmosphere, THF (2.5 mL), aryltriflate (1 mmol) and the mixture of alkyl bromides (2 mmol, 2 equiv.) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 16 h in an aluminum block. After this time, an aliquot of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was measured by GCMS. Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered through silica, and concentrated. The residue was subjected to column chromatography to yield the product as a mixture of linear/branched regioisomers (which could not be separated by column chromatography).

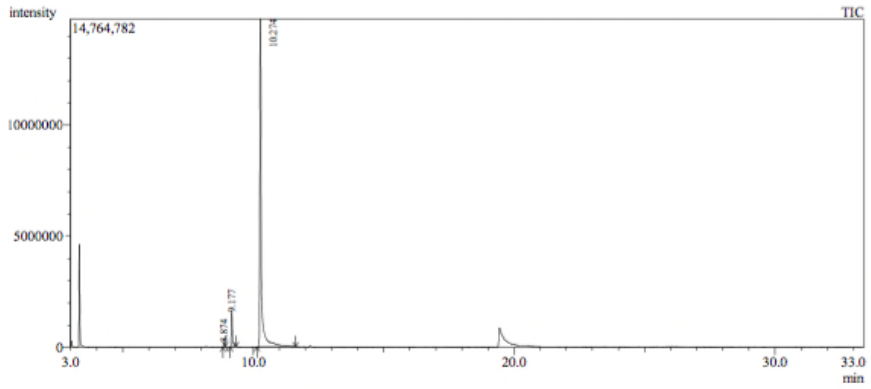
1-Pentyl-4-methoxybenzene 2-14a'

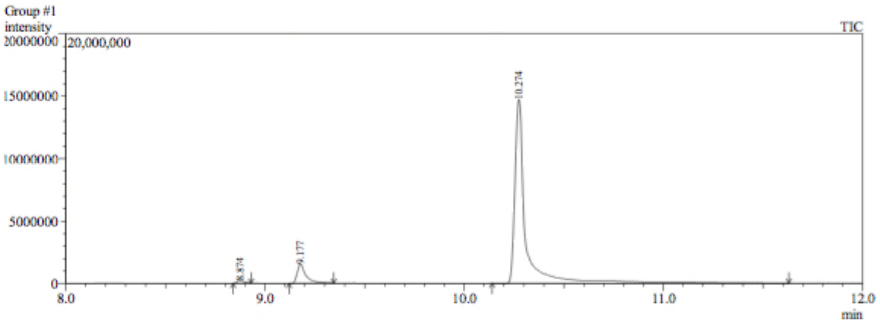


The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and the mixture of bromopentane (2-bromopentane/3-bromopentane = 79:21 from ^{1}H-NMR analysis). The ratio between the linear/branched regioisomers was determined by GCMS (linear/branched 91:9). Purification

by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 89:11) gave 137 mg (77%) of the mixture of regioisomers as pale yellow oil.

GCMS chromatogram of the crude mixture

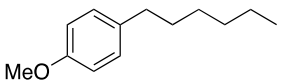




Peak Report TIC

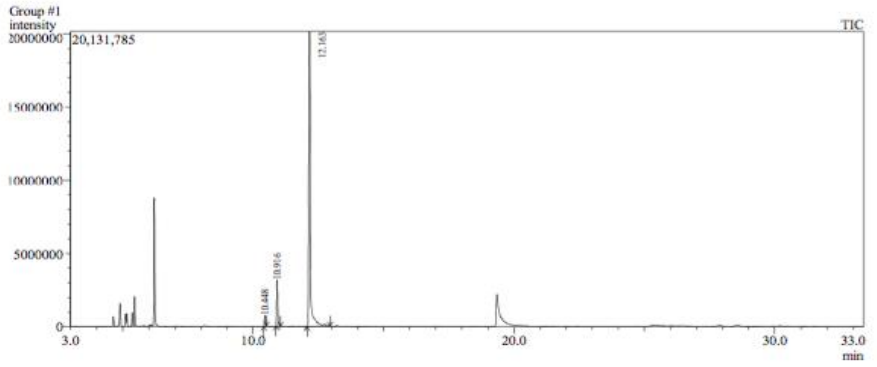
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	8.874	8.840	8.930	509809	0.85	217584	1.32	2.34	MI	
2	9.177	9.120	9.345	4657648	7.75	1557821	9.44	2.99	MI	
3	10.274	10.140	11.630	54922569	91.40	14726240	89.24	3.73	MI	
				60090026	100.00	16501645	100.00			

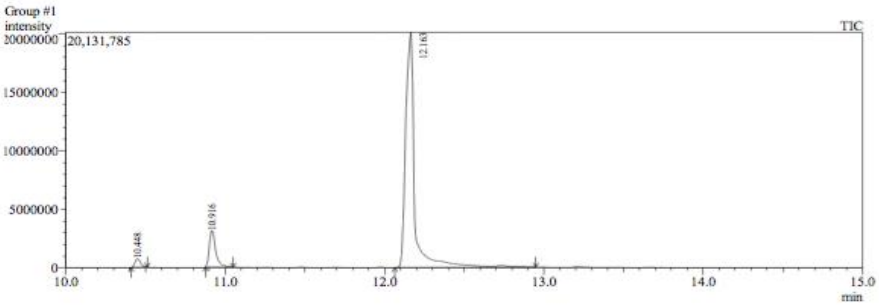
<u>1-Hexyl-4-methoxybenzene 2-14af</u>



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and the mixture of bromohexane (2-bromohexane/3-bromohexane = 59:41 from ^{1}H-NMR analysis). The ratio between the linear/branched regioisomers was determined by GCMS (linear/branched 88:12). Purification by column chromatography on silica gel (elution from pentane to pentane/ CH_2Cl_2 89:11) gave 163 mg (85%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



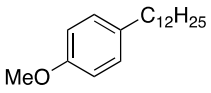


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	10.448	10.410	10.510	1777509	1.99	746943	3.11	2.38	MI	
2	10.916	10.875	11.050	8629923	9.68	3145355	13.11	2.74	MI	
3	12.163	12.065	12.950	78768478	88.33	20106419	83.78	3.92	MI	
				89175910	100.00	23998717	100.00			

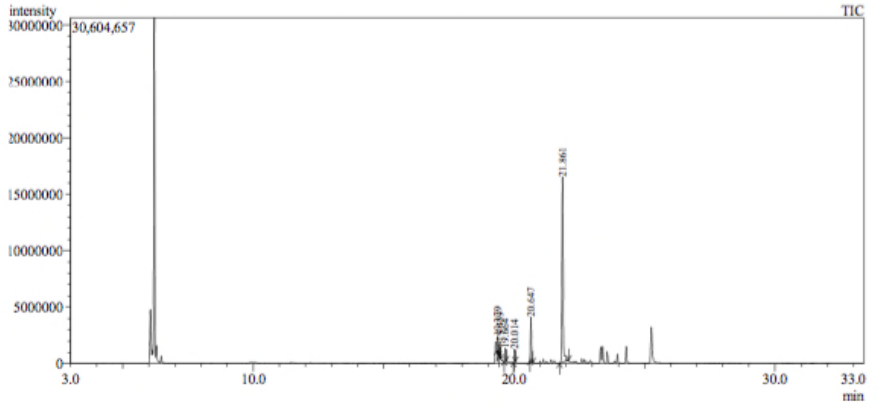
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.37 – 1.26 (m, 6H), 0.89 (t, *J* = 6.7 Hz, 3H). The spectral data is consistent with that reported in the literature.[128]

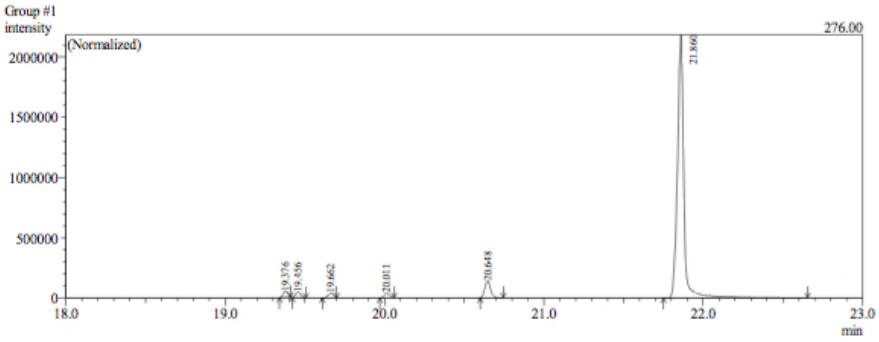
1-Methoxy-4-undecylbenzene 2-14ag



The above compound was synthesized according to the general procedure from 4-methoxyphenyl trifluoromethanesulfonate and the mixture of bromododecane (ratio of mixture of five secondary bromododecane isomers: 19:17:20:18:26 by GC-MS analysis) using Pd_2dba_3 (0.025 mmol, 22.9 mg) and phosphine **L^6** (0.05 mmol, 14.4 mg). The ratio between the linear/branched regioisomers was determined by GCMS (linear/branched 89:11). Purification by column chromatography on silica gel (elution from pentane to pentane/CH_2Cl_2 88:12) gave 198 mg (72%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report 276

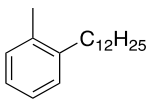
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	19.376	19.340	19.410	105828	1.56	50597	2.02	2.09	MI	
2	19.456	19.420	19.505	104628	1.54	48750	1.95	2.15	MI	
3	19.662	19.610	19.700	89106	1.31	39281	1.57	2.27	MI	
4	20.011	19.970	20.060	85772	1.27	39871	1.59	2.15	MI	
5	20.648	20.600	20.745	351863	5.19	142562	5.69	2.47	MI	
6	21.860	21.750	22.655	6038947	89.12	2182908	87.18	2.77	MI	
				6776144	100.00	2503969	100.00			

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.9 Hz, 2H), 3.79 (s, 3H), 2.54 (t, *J* = 7.6 Hz, 2H), 1.63 – 1.53 (m, 2H), 1.33 – 1.20 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H);
^{13}C NMR (100 MHz, $CDCl_3$) δ 157.7, 135.2, 129.4, 113.8, 55.4, 35.2, 32.1, 31.9, 29.8, 29.8, 29.8, 29.7, 29.7, 29.5, 29.4, 22.8, 14.3;

IR (neat): ν (cm^{-1}) 2922, 2852, 1511, 1464, 1245, 1176, 1039, 1082, 1005, 820;

GCMS (EI) m/z for $C_{19}H_{32}O$ ($[M]^{+\bullet}$): 276.

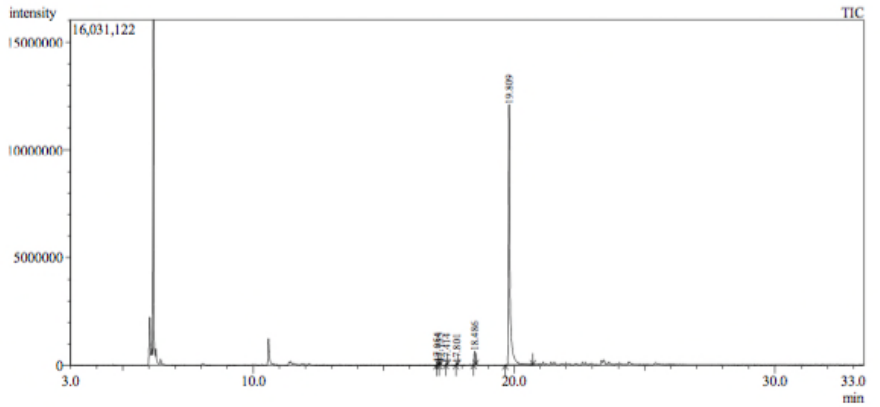
<u>1-Methyl-2-undecylbenzene 2-14ah</u>

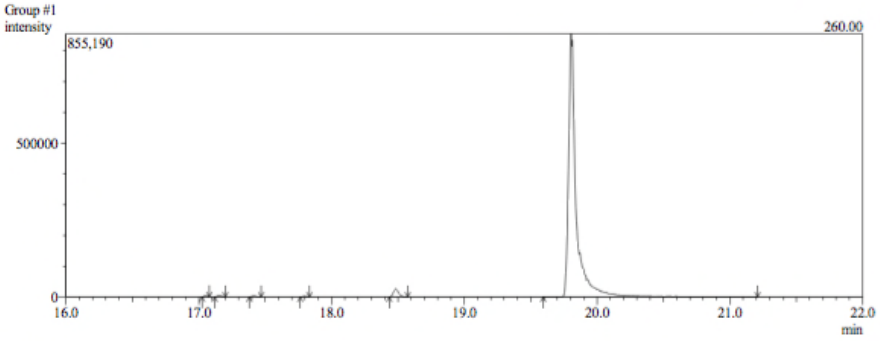


The above compound was synthesized according to the general procedure from *o*-tolyl trifluoromethanesulfonate and the mixture of bromododecane using Pd_2dba_3 (0.025 mmol,

22.9 mg) and phosphine **L^6** (0.05 mmol, 14.4 mg). The ratio between the linear/branched regioisomers was determined by GCMS (linear/branched 97:3). Purification by column chromatography on silica gel (elution using pentane) gave 169 mg (65%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture





Peak Report 260

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.052	17.025	17.080	8117	0.23	4147	0.46	1.96	MI	
2	17.155	17.120	17.200	9886	0.28	4745	0.53	2.08	MI	
3	17.413	17.380	17.470	8320	0.23	3559	0.40	2.34	MI	
4	17.800	17.765	17.835	6974	0.20	3156	0.35	2.21	MI	
5	18.482	18.435	18.575	73910	2.08	26192	2.92	2.82	MI	
6	19.805	19.595	21.210	3449983	96.99	855200	95.34	4.03	MI	
				3557190	100.00	896999	100.00			

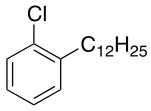
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 – 7.02 (m, 4H), 2.65 – 2.55 (m, 2H), 2.32 (s, 3H), 1.57 (dd, *J* = 15.5, 7.8 Hz, 2H), 1.38 – 1.24 (m, 18H), 0.90 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 136.0, 130.2, 128.9, 126.0, 125.8, 33.5, 32.1, 30.5, 29.9, 29.8, 29.8, 29.8, 29.8, 29.7, 29.5, 22.9, 19.4, 14.3;

IR (neat): ν (cm^{-1}) 2921, 2852, 1462, 739;

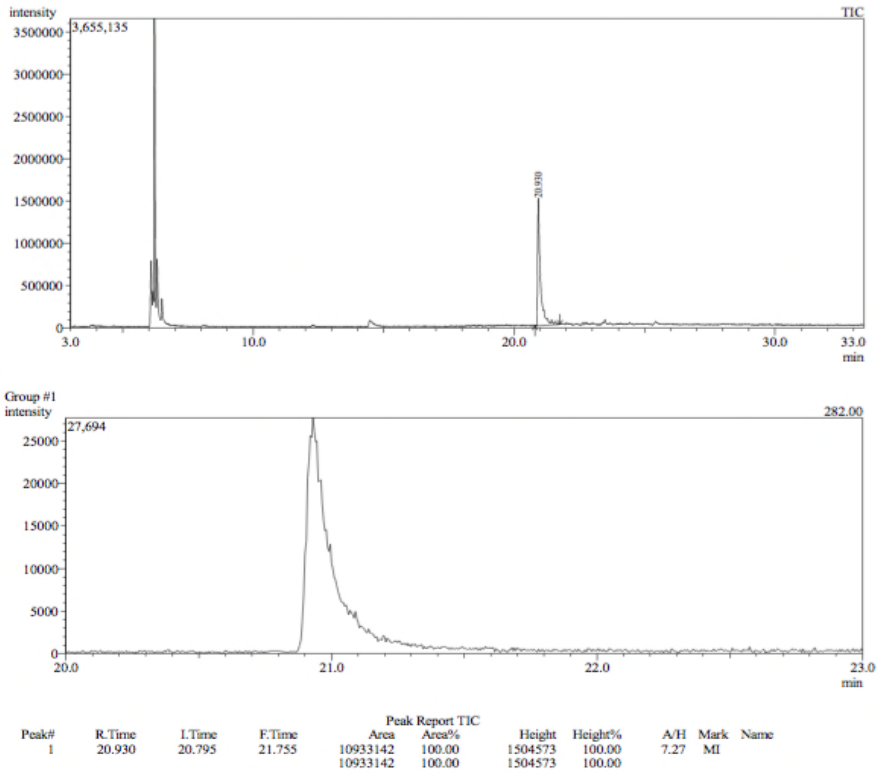
GCMS (EI) m/z for $C_{19}H_{32}$ ($[M]^{+\bullet}$): 260.

<u>1-Chloro-2-undecylbenzene 2-14ai</u>



The above compound was synthesized according to the general procedure from 2-chlorophenyl trifluoromethanesulfonate and the mixture of bromododecane. The ratio between the linear/branched regioisomers was determined by GCMS (linear/branched >99/1). Purification by column chromatography on silica gel (elution using pentane) gave 198 mg (67%) of the mixture of regioisomers as colourless oil.

GCMS chromatogram of the crude mixture



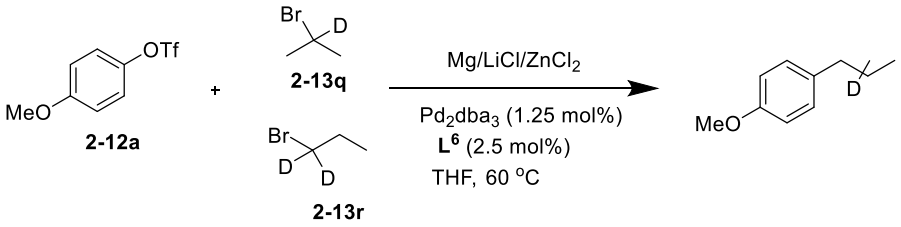
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.24 – 7.08 (m, 3H), 2.77 – 2.68 (m, 2H), 1.61 (dt, *J* = 15.4, 7.6 Hz, 2H), 1.38 – 1.24 (m, 18H), 0.89 (t, *J* = 6.9 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 134.1, 130.5, 129.5, 127.2, 126.8, 33.8, 32.1, 29.9, 29.8, 29.8, 29.8, 29.7, 29.6, 29.6, 29.5, 22.9, 14.3;

IR (neat): ν (cm^{-1}) 2921, 2852, 1466, 1443, 1051, 749;

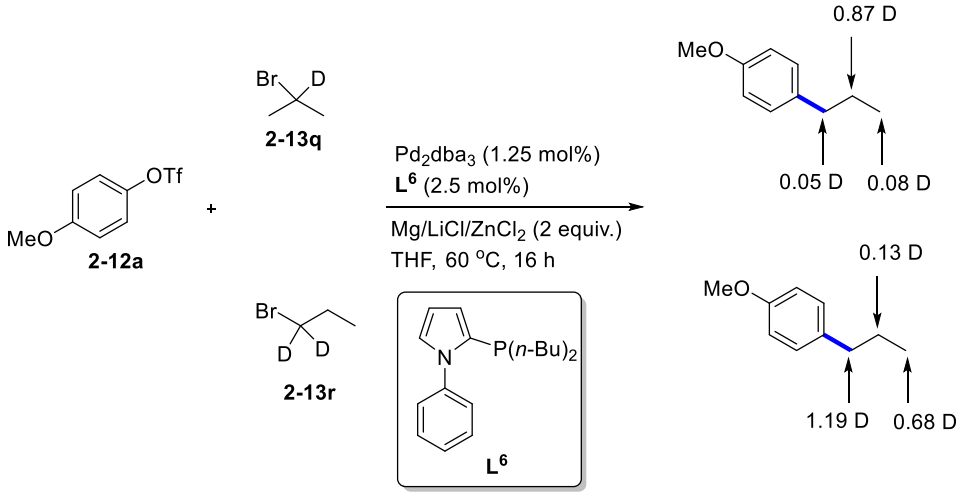
GCMS (EI) m/z for $C_{18}H_{29}Cl$ ($[M]^{+\bullet}$): 280.

^{2}H Labeling experiments



In an argon-filled glove box, Pyrex glass tube with stir bar was charged with LiCl (85 mg, 2 mmol, 2 equiv.), Mg (49 mg, 2 mmol, 2 equiv.), $ZnCl_2$ (273 mg, 2 mmol, 2 equiv.), Pd_2dba_3 (11.4 mg, 0.0125 mmol, 1.25 mol%) and phosphine **L^6** (7.2 mg, 0.025 mmol, 2.5 mol%). The tube was sealed with a septum and paraffin, and was taken out. Under an argon atmosphere, THF (2.5 mL), 4-methoxyphenyl trifluoromethanesulfonate (1 mmol, 256 mg) and either 2-bromopropane-2-d_1 (98% D) (**2-13q**) or 1-Bromopropane-1,1-d_2 (99% D) (**2-13r**) (2 mmol, 2 equiv.) was subsequently added and the flask was heated at 60 °C for 16 h in an aluminum block. After this time, an aliquot of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was measured by GCMS. Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 5 mL). The combined organic fractions were dried over $MgSO_4$, filtered through silica, and concentrated. The residue was subjected to column chromatography (elution from pentane to 88:12 pentane/CH_2Cl_2) to yield the deuterated product as a colourless oil.

Experiments with deuterated substrates: the deuterium contents were measured by ^{2}H NMR.



From 2-bromopropane-2-d_1 (**2-13q**)

^{2}H NMR (92 MHz, Chloroform-*d*) δ 2.52 (s, 0.05 D), 1.60 (s, 0.87 D), 0.93 (s, 0.08 D).

From 1-Bromopropane-1,1-d_2 (**2-13r**)

^{2}H NMR (92 MHz, Chloroform-*d*) δ 2.50 (s, 1.19 D), 1.60 (s, 0.13 D), 0.91 (s, 0.69 D).

Gram-scale synthesis of 2-14ai

In an argon-filled glove box, a Schlenck flask with stir bar was charged with LiCl (0.848 g, 20 mmol, 2 equiv.), Mg (0.486 g, 20 mmol, 2 equiv.), $ZnCl_2$ (2.73 g, 20 mmol, 2 equiv.), Pd_2dba_3 (114 mg, 0.125 mmol, 1.25 mol%) and phosphine **L^6** (72 mg, 0.25 mmol, 2.5 mol%). The flask was sealed with a septum and paraffin, and was taken out. Under an argon atmosphere, THF (25 mL), 2-chlorophenyl trifluoromethanesulfonate (10 mmol, 2.6 g) and the mixture of bromododecanes (20 mmol, 5 g, 2 equiv.) were subsequently added and the flask was heated at 60 °C for 16 h in an aluminum block. After this time, a fraction of the crude mixture was diluted with Et_2O and the ratio of linear/branched regioisomers was assessed by GCMS (linear/branched >99/1). Then, the reaction mixture was diluted with NH_4Cl sat. aq. solution (20 mL) and Et_2O (20 mL). The organic layer was removed and the aqueous fraction was extracted with Et_2O (2 x 20 mL). The combined organic fractions were dried over $MgSO_4$, filtered through silica, and concentrated. The residue was subjected to column chromatography (elution with pentane) to yield 1.7 g (61% yield) of **2-14ai** as a colourless oil.

3. Chapter 3: Direct Barbier-Negishi coupling of secondary alkyl bromides with aryl and alkenyl triflates and nonaflates

General procedure for the screening reactions (Barbier conditions)

In an argon-filled glove box, a Pyrex glass tube equipped with stirring bar was charged with LiCl (42.4 mg, 1.0 mmol, 2.0 equiv.), Mg powder (24.3 mg, 1 mmol, 2.0 equiv.), $ZnCl_2$ (136 mg, 1mmol, 2.0 equiv.), well-defined catalyst (5.0 mol%) or Pd_2dba_3 (97%) (2.5 mol%)/lignad (5.0 mol%). The tube was sealed with a septum and paraffin, and was taken out of the glove box. Under an argon atmosphere, THF (2.5 mL), *p*-methoxyphenyl trifluoromethanesulfonate (0.5 mmol) and 3-bromopentane (151 mg, 1.0 mmol, 2.0 equiv.) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 24 h in an aluminum block. After this time, dodecane was added and the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). An aliquot of the crude mixture was taken. The yield was determined by GC using dodecane as the internal standard and the ratio of direct/migrative cross-coupling products was also measured by GC.

(**Note**: Using Zn/LiCl system instead of Mg/LiCl/$ZnCl_2$ system resulted in low conversion and low yield.)

General procedure for the screening reactions (Performed using the preformed organozinc halide)

The preformed organozinc halide was prepared and titrated according to the procedures reported by Knochel and co-workers.[130]

In an argon-filled glove box, a Pyrex glass tube equipped with stirring bar was charged with well-defined catalyst (5.0 mol%) or Pd_2dba_3 (97%) (2.5 mol%)/lignad (5.0 mol%). The tube was sealed with a septum and paraffin, and was taken out of the glove box. Under an argon atmosphere, THF (to make the final concentration of the mixture to 0.2 M), *p*-methoxyphenyl trifluoromethanesulfonate (0.5 mmol) were added followed by the addition of preformed organozinc halide in THF solution at 0 ^oC. The septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 °C for 24 h in an aluminum block. After this time, dodecane was added and the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). An aliquot of the crude mixture was taken. The yield was

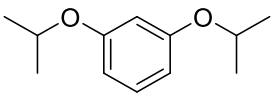
determined by GC using dodecane as the internal standard and the ratio of direct/migrative cross-coupling products was also measured by GC.

General procedure for the screening reactions (for primary alkyl bromides, using 1-Br pentane)

In an argon-filled glove box, a Pyrex glass tube equipped with stirring bar was charged with LiCl (42.4 mg, 1.0 mmol, 2.0 equiv.), Mg powder (24.3 mg, 1 mmol, 2.0 equiv.), $ZnCl_2$ (136 mg, 1mmol, 2.0 equiv.), Pd_2dba_3 (97%) (**Y** mol%)/lignad (**Z** mol%). The tube was sealed with a septum and paraffin, and was taken out of the glove box. Under an argon atmosphere, THF (2.5 mL), triflate or nonaflate (0.5 mmol, 1.0 e.q.) and 1-bromopentane (151 mg, 1.0 mmol, 2.0 equiv.) were subsequently added; the septum was quickly removed and replaced with a phenolic screw cap and the tube was heated at 60 ^oC or 40 ^oC in an aluminum block or 25 ^oC water bath for 24 h. After this time, the reaction mixture was diluted with NH_4Cl sat. aq. solution (5 mL) and Et_2O (5 mL). An aliquot of the crude mixture was measured by GC-MS to give an estimated ratio described in the following table.

Synthesis of ligands

1,3-diisopropoxybenzene



Chemical Formula: $C_{12}H_{18}O_2$
Exact Mass: 194.1307

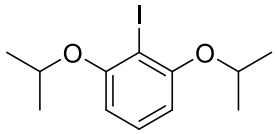
The alkylation product was prepared according to a modified procedure reported by Yasuda and co-workers.[131]

To an oven-dried argon flushed 500 mL two-necked flask was added resorcinol (22.02g, 200 mmol) and K_2CO_3 (110 g, 800 mmol). The flask was flushed and backfilled with argon three times before the addition of 2-bromopropane (75.1 mL, 800 mmol) and dry DMF (200 mL). The reaction mixture was heated to 70 ^oC and stirred for 24 h before it was cooled to room temperature and quenched with demineralized water (1000 mL) and Et_2O (200 mL). The mixture was extracted with Et_2O three times. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (Pentane/Et_2O) gave the desired product as a colourless oil (37.23g, 96%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.09 (m, 1H), 6.55 – 6.38 (m, 3H), 4.53 (hept, *J* = 6.1 Hz, 2H), 1.34 (d, *J* = 6.2 Hz, 12H).

The NMR data for this compound was consistent with literature data.

2-iodo-1,3-diisopropoxybenzene



Chemical Formula: $C_{12}H_{17}IO_2$
Exact Mass: 320.0273

The iodination step was performed according to a modified procedure reported by Koning and co-workers.[132]

To a solution of 1,3-diisopropoxybenzene (13.6 g, 70 mmol) in THF (100 mL) in an oven dried argon flushed two-necked flask at 0 ^{o}C was added *n*-BuLi solution (77 mmol). The reaction mixture was stirred for 1 h at room temperature before it was cooled to 0 ^{o}C. Then, a solution of iodine (19.5 g, 77 mmol) in THF (100 mL) was added dropwise and the mixture was stirred for further 4 h at room temperature. After that time, demineralized water (200 mL) was added and the mixture was extracted with EtOAc (4 x 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (pentane/CH_2Cl_2) gave the desired product as a pale yellow oil (17.6 g, 78%).

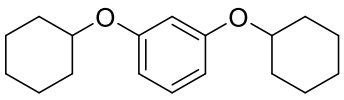
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.23 – 7.14 (m, 1H), 6.51 – 6.44 (m, 2H), 4.56 (hept, *J* = 6.2 Hz, 2H), 1.40 (d, *J* = 6.2 Hz, 12H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.5, 129.3, 107.2, 83.1, 72.1, 22.3.

IR (neat): ν (cm^{-1}) 2976, 2930, 1584, 1454, 1245, 1107, 1053, 762, 706.

HRMS (ESI): Calcd for $C_{12}H_{17}INaO_2$ $[M+Na]^+$: 343.0165, found: 343.0160**.**

1,3-bis(cyclohexyloxy)benzene



Chemical Formula:
$C_{18}H_{26}O_2$
Exact Mass: 274.1933

The product was synthesized according to the procedure reported by Yasuda and co-workers.[131]

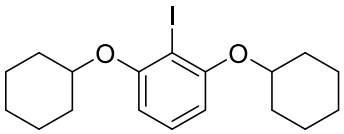
DIAD (25 g, 123 mmol, 2.72 e.q.) in toluene (37.5 mL) was added to a solution of resorcinol (5.0 g, 45.4 mmol, 1.0 e.q.), cyclohexanol (13.6 g, 136 mmol, 3.0 e.q.) and triphenylphosphine (35g, 133 mmol, 2.94 e.q.) in THF (50 mL) at 0 °C. The mixture was stirred for 24 h at room temperature. After that time, hydrogen peroxide (30%, around 15 mL) was added to the mixture to oxidize unreacted triphenylphosphine, followed by addition of cyclohexane resulting in precipitation of triphenylphosphine oxide, which then was removed by filtration. The aqueous layer was separated and extracted with cyclohexane two times. The combined organic layers were washed with sodium hydroxide solution (1 M, 3 times). The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography, affording the desired product as a pale yellow oil (5.6 g, 45%).
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.07 (m, 1H), 6.55 – 6.41 (m, 3H), 4.27 – 4.13 (m, 2H), 2.08 – 1.91 (m, 4H), 1.87 – 1.75 (m, 4H), 1.62 – 1.46 (m, 6H), 1.42 – 1.28 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 159.2, 129.8, 108.2, 104.4, 75.5, 32.0, 25.8, 24.0.

IR (neat): ν (cm^{-1}) 2933, 2857, 1597, 1486, 1370, 1282, 1142, 1052, 838, 759, 688.

HRMS (ESI): Calcd for $C_{18}H_{27}O_2$ $[M+H]^+$: 275.2006, found: 275.2003.

<u>((2-iodo-1,3-phenylene)bis(oxy))dicyclohexane</u>



Chemical Formula:
$C_{18}H_{25}IO_2$
Exact Mass: 400.0899

To a solution of 1,3-bis(cyclohexyloxy)benzene (5.49 g, 20 mmol) in THF (50 mL) in an oven dried argon flushed two-necked flask at 0 °C was added *n*-BuLi solution (22 mmol). The reaction mixture was stirred for 3 h at 0 °C and 1 h at room temperature before it was cooled

to 0 °C again. Then, a solution of iodine (5.58 g, 22 mmol) in THF (50 mL) was added dropwise and the mixture was stirred at room temperature overnight. After that time, saturated $Na_2S_2O_3$ solution was added and the mixture was extracted with EtOAc (4 x 50 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (pentane/CH_2Cl_2) gave the desired product as a pale yellow oil (5.6 g, 70%).

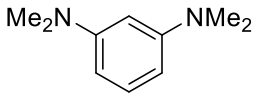
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.07 (m, 1H), 6.51 – 6.36 (m, 2H), 4.43 – 4.25 (m, 2H), 1.97 – 1.79 (m, 8H), 1.77 – 1.64 (m, 4H), 1.58 – 1.48 (m, 2H), 1.47 – 1.32 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.3, 129.2, 106.9, 82.9, 76.6, 31.6, 25.8, 23.4.

IR (neat): ν (cm^{-1}) 2933, 2857, 1582, 1457, 1248, 1075, 761, 706**.**

HRMS (ESI): Calcd for $C_{18}H_{26}IO_2$ $[M+H]^+$: 401.0972, found: 401.0976**.**

<u>*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine</u>



Chemical Formula: $C_{10}H_{16}N_2$
Exact Mass: 164.1313

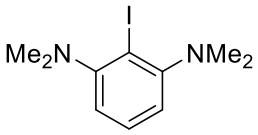
In the glovebox, an oven dried argon flushed flask was charged with $PdCl_2$ (74.1 mg, 0.418 mmol) and JosiphosSL-J009-1 (268 mg, 0.418 mmol). Dry and degassed DME (100 mL) was added to the reaction mixture. The latter was then stirred for 10 min before dimethylamine (62.7 mL, 2.0 M in THF, 125 mmol) and 1,3-dichlorobenzene (2.40 mL, 20.9 mmol) was added. The mixture was cooled to 0 °C and LiHMDS (62.7 mL, 1.0 M in THF, 62.7 mmol) was slowly added. After the addition, the ice bath was removed and the reaction mixture was stirred for 16 h at room temperature. The mixture was quenched with demineralized water (100 mL) and extracted with EtOAc (3 x 80 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (Cyclohexane/Ethyl acetate) gave the product as a pale orange oil (3.45 g, 99.9%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 7.19 – 7.13 (m, 1H), 6.27 – 6.21 (m, 2H), 6.17 – 6.13 (m, 1H), 2.98 (s, 12H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 151.9, 129.6, 102.7, 98.0, 41.0.

The NMR data for this compound was consistent with literature datas.[133]

2-iodo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula: $C_{10}H_{15}IN_2$
Exact Mass: 290.0280

To an oven dried argon flushed flask was added a solution of *N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine (164 mg, 1.0 mmol) in hexane (2.0 mL) and *s*-BuLi (1.1 mmol). The mixture was stirred for 1 h at 80 ^{o}C. The heating was turned off and 1-chloro-2-iodoethane (0.109 mL, 1.2 mmol) was slowly added. The mixture was stirred for a further 30 min at 80 ^{o}C before it was cooled to room temperature and quenched with a saturated NH_4Cl solution (8.0 mL). The mixture was extracted with EtOAc three times. The combined organic phases were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude was diluted with cyclohexane/EtOAc (1/1, 30 mL) and filtered through a short plug of Celite to yield the product as a brown solid (263 mg, 91%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.29 – 7.22 (m, 1H), 6.88 – 6.84 (m, 2H), 2.70 (s, 12H).

^{13}C NMR (126 MHz, Acetone-d_6) δ 158.0, 130.5, 116.8, 101.6, 45.6.

IR (neat): ν (cm^{-1}) 2979, 2937, 2824, 2779, 1573, 1461, 1301, 1003, 791, 723.

HRMS (ESI): Calcd for $C_{10}H_{16}IN_2$ $[M+H]^+$: 291.0353, found: 291.0351.

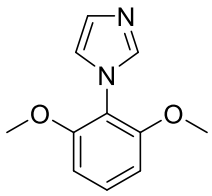
m.p.: 30-32 ^{o}C.

General procedure A for the Ulmann coupling of azoles

In the glovebox, an oven-dried argon flushed flask was charged with CuI (98%) (0.2 e.q.), Cs_2CO_3 (2.5 e.q.) and azoles (1.6 e.q.). Then outside the glovebox, a solution of 2-iodo-1,3-disubstituted benzene (1.0 e.q.) in DMSO (0.5 M) was added to the flask under argon. The flask was sealed and stirred at 120 ^{o}C for 72 h under vigorous stirring. After that time, the mixture was cooled to room temperature, diluted with cyclohexane/EtOAc (1/1) and filtered over a plug of Celite. The mixture was extracted with ice cold brine three times and the aqueous phase was re-extracted with EtOAc two times. The combined organic phases

were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (cyclohexane/EtOAc) gave the desired coupling product.

1-(2,6-dimethoxyphenyl)-1*H*-imidazole



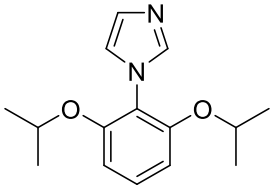
Chemical Formula:
$C_{11}H_{12}N_2O_2$
Exact Mass: 204.0899

Obtained according to the **general procedure A** on 6.0 mmol scale (0.61 g, 50% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.60 – 7.53 (m, 1H), 7.36 – 7.29 (m, 1H), 7.21 – 7.15 (m, 1H), 7.05 – 6.99 (m, 1H), 6.74 – 6.60 (m, 2H), 3.78 (s, 6H).

The NMR data for this compound was consistent with literature data.[134]

1-(2,6-diisopropoxyphenyl)-1*H*-imidazole



Chemical Formula:
$C_{15}H_{20}N_2O_2$
Exact Mass: 260.1525

Obtained according to the **general procedure A** on 2.0 mmol scale (0.418 g, 80% yield).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.55 – 7.45 (m, 1H), 7.36 – 7.26 (m, 1H), 7.10 – 7.03 (m, 1H), 7.02 – 6.95 (m, 1H), 6.85 – 6.75 (m, 2H), 4.54 (hept, *J* = 6.1 Hz, 2H), 1.19 (d, *J* = 6.0 Hz, 12H).

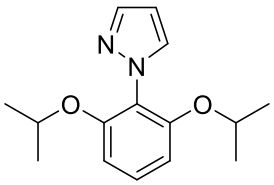
^{13}C NMR (126 MHz, Acetone-d_6) δ 154.8, 139.6, 130.0, 128.4, 122.1, 119.3, 108.6, 72.3, 22.3.

IR (neat): ν (cm^{-1}) 2977, 2932, 1594, 1509, 1471, 1252, 1110, 1054, 777, 730.

HRMS (ESI): Calcd for $C_{15}H_{21}N_2O_2$ $[M+H]^+$: 261.1598, found: 261.1601.

m.p.: 55-58 ºC.

1-(2,6-diisopropoxyphenyl)-1*H*-pyrazole



Chemical Formula:
$C_{15}H_{20}N_2O_2$
Exact Mass: 260.1525

Obtained according to the **general procedure A** on 2.0 mmol scale (0.278 g, 53% yield).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.59 – 7.55 (m, 1H), 7.54 – 7.48 (m, 1H), 7.34 – 7.27 (m, 1H), 6.79 – 6.74 (m, 2H), 6.37 – 6.29 (m, 1H), 4.45 (hept, *J* = 6.1 Hz, 2H), 1.14 (d, *J* = 6.1 Hz, 12H).

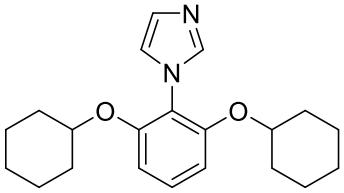
^{13}C NMR (126 MHz, Acetone-d_6) δ 156.5, 139.8, 133.1, 130.5, 123.9, 109.4, 105.6, 72.6, 22.4.

IR (neat): ν (cm^{-1}) 2976, 2931, 1592, 1522, 1471, 1251, 1110, 1066, 779, 738.

HRMS (ESI): Calcd for $C_{15}H_{20}N_2NaO_2$ $[M+Na]^+$: 283.1417, found: 283.1413.

m.p.: 30-32 ºC.

1-(2,6-bis(cyclohexyloxy)phenyl)-1*H*-imidazole



Chemical Formula:
$C_{21}H_{28}N_2O_2$
Exact Mass: 340.2151

Obtained according to the **general procedure A** on 2.0 mmol scale (0.501 g, 73% yield).

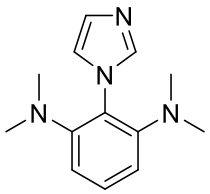
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.55 (m, 1H), 7.24 – 7.17 (m, 1H), 7.14 – 7.10 (m, 1H), 7.07 – 7.02 (m, 1H), 6.66 – 6.59 (m, 2H), 4.23 – 4.14 (m, 2H), 1.82 – 1.71 (m, 4H), 1.63 – 1.54 (m, 4H), 1.50 – 1.39 (m, 6H), 1.31 – 1.22 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.7, 139.1, 128.8, 127.6, 121.4, 118.6, 107.6, 76.6, 31.5, 25.6, 23.2.

IR (neat): ν (cm^{-1}) 2933, 2858, 1594, 1511, 1470, 1251, 1079, 956, 903, 777, 730, 662.

HRMS (ESI): Calcd for $C_{21}H_{29}N_2O_2$ $[M+H]^+$: 341.2224, found: 341.2222.

2-(1*H*-imidazol-1-yl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula: $C_{13}H_{18}N_4$
Exact Mass: 230.1531

In the glovebox, a 5.0 mL microwave vial equipped with a stirring bar was charged with CuI (99.999%) (38.1 mg, 0.2 mmol), Cs_2CO_3 (815 mg, 2.5 mmol) and imidazole (109 mg, 1.6 mmol). Then outside the glovebox, a solution of 2-iodo-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine (290 mg, 1.0 mmol) in DMSO (3.0 mL) was added under argon. The vial was sealed and shaked before heating it in the microwave for 9 h at 160 ^{o}C. After that time, the mixture was diluted with cyclohexane/EtOAc (1/1, 20 mL) and filtered through a plug of Celite. The mixture was extracted with ice cold brine twice and the aqueous phase was re-extracted with EtOAc twice. The combined organic phases were dried over $MgSO_4$ and the solvent was removed *in vacuo*. Purification by silica gel column chromatography (Cyclohexane/EtOAc to EtOAc) gave the product as a pale yellow solid (111 mg, 48%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.67 – 7.57 (m, 1H), 7.27 – 7.21 (m, 1H), 7.19 – 7.15 (m, 1H), 7.11 – 7.04 (m, 1H), 6.90 – 6.73 (m, 2H), 2.37 (s, 12H).

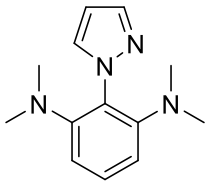
^{13}C NMR (126 MHz, Acetone-d_6) δ 151.2, 139.3, 129.7, 129.4, 124.4, 121.1, 114.0, 43.1.

IR (neat): ν (cm^{-1}) 3106, 2844, 2836, 2790, 1582, 1479, 1294, 1046, 1006, 798, 741.

HRMS (ESI): Calcd for $C_{13}H_{19}N_4$ $[M+H]^+$: 231.1604, found: 231.1602.

m.p.: 126-128 ^{o}C.

***N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethyl-2-(1*H*-pyrazol-1-yl)benzene-1,3-diamine**



Chemical Formula: $C_{13}H_{18}N_4$
Exact Mass: 230.1531

In the glovebox, an oven-dried argon flushed flask was charged with CuI (98%) (57.1 mg, 0.3 mmol), Cs_2CO_3 (815 mg, 2.5 mmol), LiI (268 mg, 2.0 mmol) and pyrazole (109 mg, 1.6 mmol). Then outside the glovebox, a solution of 2-iodo-N^1,N^1,N^3,N^3-tetramethylbenzene-1,3-diamine (1.0 mmol) in DMSO (2.0 mL) was added to the flask under argon. The flask was sealed and stirred at 120 ºC for 72 h under vigorous stirring. After that time, the mixture was cooled to room temperature, diluted with cyclohexane/EtOAc (1/1) and filtered over a plug of Celite. The mixture was extracted with ice cold brine three times and the aqueous phase was re-extracted with EtOAc two times. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. Purification by silica gel column chromatography (cyclohexane/EtOAc) gave the desired product as a white solid (126 mg, 55%).

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.66 – 7.63 (m, 1H), 7.61 – 7.58 (m, 1H), 7.26 – 7.20 (m, 1H), 6.74 – 6.70 (m, 2H), 6.44 – 6.41 (m, 1H), 2.38 (s, 12H).

^{13}C NMR (126 MHz, Acetone-d_6) δ 152.2, 140.2, 133.9, 130.0, 127.3, 113.1, 106.9, 43.4.

IR (neat): ν (cm^{-1}) 2925, 2836, 2787, 1584, 1482, 1317, 1017, 790, 741.

HRMS (ESI): Calcd for $C_{13}H_{19}N_4$ $[M+H]^+$: 231.1604, found: 231.1606.

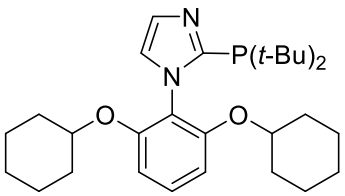
General procedure B for the synthesis of azole-based phosphine ligands

The phosphine ligands were prepared following a modified procedure of Beller and co-workers.[78a]

An oven-dried argon flushed flask was charged with the corresponding aryl-1*H*-azole (1.0 e.q., 0.5 M in THF). The mixture was cooled to -30 ºC. Then, *n*-BuLi (1.0 e.q.) was added slowly and the mixture was stirred for 30 min at that temperature. A solution of the corresponding dialkylchlorophosphine (1.1 e.q.) in THF (2.0 M) was added dropwise before warming the mixture up to room temperature and stirring it for 1 h at 50 ºC. After cooling with ice bath,

degassed saturated NH_4Cl solution was added and the mixture was extracted with degassed toluene three times. The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification by silica gel column chromatography (Cyclohexane/EtOAc) provided the corresponding azole-based phosphine ligands.

1-(2,6-bis(cyclohexyloxy)phenyl)-2-(di-*tert*-butylphosphaneyl)-1*H*-imidazole



Chemical Formula:
$C_{29}H_{45}N_2O_2P$
Exact Mass: 484.3219

Obtained as a white solid (203.6 mg, 42% yield) according to the **general procedure B** on 1.0 mmol scale.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.40 – 7.30 (m, 1H), 7.26 – 7.19 (m, 1H), 6.91 – 6.83 (m, 1H), 6.60 – 6.51 (m, 2H), 4.21 – 4.11 (m, 2H), 1.96 – 1.83 (m, 2H), 1.79 – 1.68 (m, 2H), 1.67 – 1.23 (m, 16H), 1.22 (s, 9H), 1.19 (s, 9H).

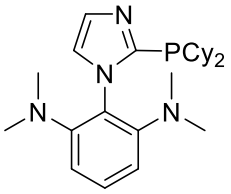
^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.0, 148.7 (d, *J* = 19.0 Hz), 129.6, 129.2, 123.9, 119.3, 106.4, 76.8, 33.2 (d, *J* = 16.0 Hz), 32.2, 31.4, 30.8, 30.6, 25.6, 23.7 (d, *J* = 3.8 Hz).

^{31}P NMR (162 MHz, Chloroform-*d*) δ 8.3.

IR (neat): ν (cm^{-1}) 2935, 2857, 1594, 1469, 1363, 1254, 1080, 961, 778, 740.

HRMS (ESI): Calcd for $C_{29}H_{46}N_2O_2P$ $[M+H]^+$: 485.3291, found: 485.3296.

2-(2-(dicyclohexylphosphaneyl)-1*H*-imidazol-1-yl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula:
$C_{25}H_{39}N_4P$
Exact Mass: 426.2912

Obtained as a white solid (210 mg, 63% yield) according to the **general procedure B** on 0.782 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.28 – 7.25 (m, 1H), 7.25 – 7.23 (m, 2H), 6.85 – 6.82 (m, 2H), 2.41 (s, 12H), 2.20 – 2.07 (m, 4H), 1.80 – 1.72 (m, 2H), 1.69 – 1.61 (m, 6H), 1.28 – 1.16 (m, 8H), 1.15 – 1.09 (m, 2H).

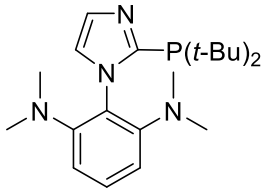
^{13}C NMR (101 MHz, Acetone-d_6) δ 152.1, 149.2 (d, J = 14.0 Hz), 130.8, 129.9, 126.3, 124.8, 114.4, 44.0, 35.4 (d, J = 10.0 Hz), 32.3 (d, J = 17.1 Hz), 28.5 (d, J = 12.2 Hz), 28.1 (d, J = 8.4 Hz), 27.4 (d, J = 0.9 Hz).

^{31}P NMR (162 MHz, Acetone-d_6) δ -21.9.

IR (neat): ν (cm^{-1}) 2921, 2848, 1584, 1480, 1447, 1016, 738.

HRMS (ESI): Calcd for $C_{25}H_{40}N_4P$ $[M+H]^+$: 427.2985, found: 427.2986.

2-(2-(di-*tert*-butylphosphaneyl)-1*H*-imidazol-1-yl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula: $C_{21}H_{35}N_4P$
Exact Mass: 374.2599

Obtained as a white solid (114 mg, 41% yield) according to the **general procedure B** on 0.738 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.48 – 7.43 (m, 1H), 7.33 – 7.25 (m, 2H), 6.91 – 6.85 (m, 2H), 2.46 (s, 12H), 1.16 (s, 9H), 1.13 (s, 9H).

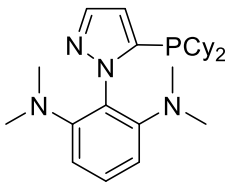
^{13}C NMR (126 MHz, Acetone-d_6) δ 152.9, 149.1 (d, J = 24.5 Hz), 130.2, 129.7, 127.3, 125.8, 115.4, 45.2, 33.6 (d, J = 19.2 Hz), 31.0 (d, J = 15.3 Hz).

^{31}P NMR (202 MHz, Acetone-d_6) δ 10.5.

IR (neat): ν (cm^{-1}) 3086, 2921, 2855, 1583, 1472, 1018, 791, 741.

HRMS (ESI): Calcd for $C_{21}H_{36}N_4P$ $[M+H]^+$: 375.2672, found: 375.2676.

2-(5-(dicyclohexylphosphaneyl)-1*H*-pyrazol-1-yl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula: $C_{25}H_{39}N_4P$
Exact Mass: 426.2912

Obtained as a white solid (46 mg, 13% yield) according to the **general procedure B** on 0.803 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.74 – 7.65 (m, 1H), 7.31 – 7.26 (m, 1H), 6.79 – 6.75 (m, 2H), 6.60 – 6.56 (m, 1H), 2.52 (s, 12H), 1.79 – 1.65 (m, 12H), 1.27 – 1.08 (m, 10H).

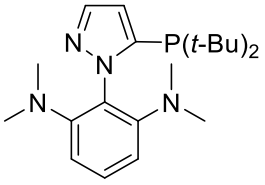
^{13}C NMR (126 MHz, Acetone-d_6) δ 153.8, 142.8 (d, *J* = 18.6 Hz), 139.5 (d, *J* = 2.3 Hz), 130.6, 129.6, 114.0, 112.2 (d, *J* = 4.1 Hz), 45.0, 35.1 (d, *J* = 11.3 Hz), 30.8 (d, *J* = 11.9 Hz), 30.7 (d, *J* = 15.1 Hz), 28.2 (d, *J* = 4.7 Hz), 28.1 (d, *J* = 6.4 Hz), 27.4 (d, *J* = 0.7 Hz).

^{31}P NMR (202 MHz, Acetone-d_6) δ -25.8.

IR (neat): ν (cm^{-1}) 2923, 2850, 1574, 1481, 1016, 740.

HRMS (ESI): Calcd for $C_{25}H_{40}N_4P$ $[M+H]^+$: 427.2985, found: 427.2980.

2-(5-(di-*tert*-butylphosphaneyl)-1*H*-pyrazol-1-yl)-*N*^{1},*N*^{1},*N*^{3},*N*^{3}-tetramethylbenzene-1,3-diamine



Chemical Formula: $C_{21}H_{35}N_4P$
Exact Mass: 374.2599

Obtained as a white solid (80 mg, 21% yield) according to the **general procedure B** on 1.03 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.77 – 7.66 (m, 1H), 7.33 – 7.27 (m, 1H), 6.83 – 6.80 (m, 2H), 6.77 – 6.75 (m, 1H), 2.51 (s, 12H), 1.13 (s, 9H), 1.11 (s, 9H).

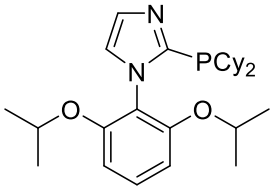
^{13}C NMR (126 MHz, Acetone-d_6) δ 154.0, 142.1 (d, *J* = 26.3 Hz), 138.8 (d, *J* = 2.2 Hz), 130.6, 130.0, 114.4, 113.8 (d, *J* = 4.6 Hz), 45.4, 32.8 (d, *J* = 20.7 Hz), 30.9 (d, *J* = 15.5 Hz).

^{31}P NMR (162 MHz, Acetone-d_6) δ 6.1.

IR (neat): ν (cm^{-1}) 2938, 2859, 1583, 1474, 1015, 788, 740.

HRMS (ESI): Calcd for $C_{21}H_{36}N_4P$ $[M+H]^+$: 375.2672, found: 375.2675.

2-(dicyclohexylphosphaneyl)-1-(2,6-diisopropoxyphenyl)-1*H*-imidazole



Chemical Formula:
$C_{27}H_{41}N_2O_2P$
Exact Mass: 456.2906

Obtained as a white solid (199 mg, 62% yield) according to the **general procedure B** on 0.707 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.34 – 7.26 (m, 1H), 7.19 – 7.15 (m, 1H), 6.96 – 6.88 (m, 1H), 6.73 – 6.66 (m, 2H), 4.56 (hept, *J* = 6.0 Hz, 2H), 2.09 – 2.06 (m, 1H), 2.04 – 2.00 (m, 1H), 1.85 – 1.78 (m, 2H), 1.76 – 1.54 (m, 9H), 1.31 – 1.25 (m, 2H), 1.24 (d, *J* = 6.0 Hz, 6H), 1.22 – 1.13 (m, 6H), 1.12 (d, *J* = 6.0 Hz, 6H), 1.11 – 1.06 (m, 1H).

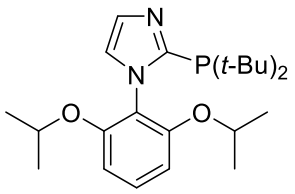
^{13}C NMR (101 MHz, Acetone-d_6) δ 155.8, 148.9 (d, *J* = 12.8 Hz), 130.4, 130.3, 124.3, 119.2, 106.8, 71.3, 35.0 (d, *J* = 8.5 Hz), 30.8 (d, *J* = 10.3 Hz), 30.7 (d, *J* = 4.7 Hz), 27.9 (d, *J* = 8.7 Hz), 27.8 (d, *J* = 5.9 Hz), 27.4, 22.4, 22.3.

^{31}P NMR (162 MHz, Chloroform-*d*) δ -22.7.

IR (neat): ν (cm^{-1}) 2939, 2860, 1583, 1474, 1014, 786, 739.

HRMS (ESI): Calcd for $C_{27}H_{42}N_2O_2P$ $[M+H]^+$: 457.2978, found: 457.2982.

2-(di-*tert*-butylphosphaneyl)-1-(2,6-diisopropoxyphenyl)-1*H*-imidazole



Chemical Formula:
$C_{23}H_{37}N_2O_2P$
Exact Mass: 404.2593

Obtained as a pale yellow solid (170 mg, 45% yield) according to the **general procedure B** on 0.945 mmol scale.

^{1}H NMR (400 MHz, Acetone-d_6) δ 7.34 – 7.27 (m, 1H), 7.23 – 7.16 (m, 1H), 7.00 – 6.91 (m, 1H), 6.73 – 6.67 (m, 2H), 4.54 (hept, *J* = 6.1 Hz, 2H), 1.22 (d, *J* = 6.1 Hz, 6H), 1.20 (s, 9H), 1.17 (s, 9H), 1.10 (d, *J* = 6.1 Hz, 6H).

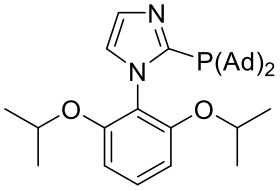
^{13}C NMR (101 MHz, Acetone-d_6) δ 156.1, 149.2 (d, *J* = 19.1 Hz), 130.5, 130.0, 124.8 (d, *J* = 1.8 Hz), 120.0, 107.2, 72.0, 33.7 (d, *J* = 17.4 Hz), 31.2 (d, *J* = 14.9 Hz), 22.6, 22.5.

^{31}P NMR (162 MHz, Acetone-d_6) δ 7.0.

IR (neat): ν (cm^{-1}) 2924, 2858, 1595, 1470, 1114, 1068, 786, 739.

HRMS (ESI): Calcd for $C_{23}H_{38}N_2O_2P$ $[M+H]^+$: 421.2665, found: 421.2669.

2-(diadamantan-1-yl)phosphaneyl)-1-(2,6-diisopropoxyphenyl)-1*H*-imidazole



Chemical Formula: $C_{35}H_{49}N_2O_2P$
Exact Mass: 560.3532

Obtained as a white solid (127 mg, 45% yield) according to the **general procedure B** on 0.5 mmol scale.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.20 (m, 1H), 7.20 – 7.06 (m, 1H), 6.82 – 6.63 (m, 1H), 6.54 – 6.28 (m, 2H), 4.48 – 4.13 (m, 2H), 1.97 (d, *J* = 12.4 Hz, 6H), 1.77 (s, 12H), 1.55 (s, 12H), 1.13 (d, *J* = 6.1 Hz, 6H), 1.00 (d, *J* = 6.1 Hz, 6H).

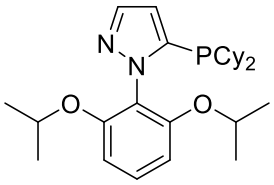
^{13}C NMR (101 MHz, Chloroform-*d*) δ 155.1, 146.4 (d, *J* = 17.7 Hz), 129.6, 129.5, 123.7, 119.0, 105.9, 71.1, 41.2 (d, *J* = 11.7 Hz), 37.5 (d, *J* = 16.2 Hz), 37.1, 28.9 (d, *J* = 8.8 Hz), 22.1 (d, *J* = 11.3 Hz) (observed complexity due to P–C splitting).

^{31}P NMR (162 MHz, Chloroform-*d*) δ 6.9.

IR (neat): ν (cm^{-1}) 2903, 2854, 1597, 1470, 1299, 1255, 1115, 1070, 972, 733.

HRMS (ESI): Calcd for $C_{35}H_{50}N_2O_2P$ $[M+H]^+$: 561.3604, found: 561.3613.

5-(dicyclohexylphosphaneyl)-1-(2,6-diisopropoxyphenyl)-1*H*-pyrazole



Chemical Formula:
$C_{27}H_{41}N_2O_2P$
Exact Mass: 456.2906

Obtained as a white solid (267 mg, 59% yield) according to the **general procedure B** on 1.0 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.71 – 7.54 (m, 1H), 7.35 – 7.23 (m, 1H), 6.71 – 6.66 (m, 2H), 6.54 – 6.51 (m, 1H), 4.50 (hept, *J* = 6.1 Hz, 2H), 1.85 – 1.77 (m, 2H), 1.76 – 1.63 (m, 10H), 1.33 – 1.23 (m, 4H), 1.21 (d, *J* = 6.1 Hz, 6H), 1.19 – 1.10 (m, 6H), 1.07 (d, *J* = 6.1 Hz, 6H).

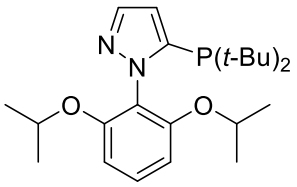
^{13}C NMR (126 MHz, Acetone-d_6) δ 157.0, 142.2 (d, *J* = 17.0 Hz), 139.9 (d, *J* = 2.5 Hz), 130.6, 123.1, 111.5 (d, *J* = 4.0 Hz), 107.9, 71.9, 35.0 (d, *J* = 10.2 Hz), 31.0 (d, *J* = 16.0 Hz), 30.8 (d, *J* = 9.7 Hz), 28.0 (d, *J* = 11.5 Hz), 27.9 (d, *J* = 8.4 Hz), 27.4 (d, *J* = 1.1 Hz), 22.6, 22.5.

^{31}P NMR (202 MHz, Acetone-d_6) δ -27.3.

IR (neat): ν (cm^{-1}) 2975, 2851, 1591, 1472, 1114, 777, 737.

HRMS (ESI): Calcd for $C_{27}H_{42}N_2O_2P$ $[M+H]^+$: 457.2978, found: 457.2976.

5-(di-*tert*-butylphosphaneyl)-1-(2,6-diisopropoxyphenyl)-1*H*-pyrazole



Chemical Formula: $C_{23}H_{37}N_2O_2P$
Exact Mass: 404.2593

Obtained as a pale yellow solid (160 mg, 40% yield) according to the **general procedure B** on 1.0 mmol scale.

^{1}H NMR (500 MHz, Acetone-d_6) δ 7.68 – 7.62 (m, 1H), 7.34 – 7.26 (m, 1H), 6.73 – 6.72 (m, 1H), 6.71 – 6.68 (m, 2H), 4.48 (hept, *J* = 6.1 Hz, 2H), 1.20 (d, *J* = 6.0 Hz, 6H), 1.18 (s, 9H), 1.15 (s, 9H), 1.05 (d, *J* = 6.0 Hz, 6H).

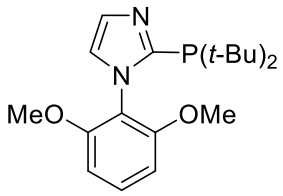
^{13}C NMR (126 MHz, Acetone-d_6) δ 157.1, 142.2 (d, *J* = 23.0 Hz), 139.5 (d, *J* = 2.2 Hz), 130.7, 123.9, 113.0 (d, *J* = 4.3 Hz), 108.4, 72.6, 32.9 (d, *J* = 19.2 Hz), 31.3 (d, *J* = 15.4 Hz), 22.6, 22.6.

^{31}P NMR (162 MHz, Acetone-d_6) δ 4.5.

IR (neat): ν (cm^{-1}) 2976, 2937, 2894, 1589, 1470, 1253, 1112, 1063, 782, 733.

HRMS (ESI): Calcd for $C_{23}H_{38}N_2O_2P$ $[M+H]^+$: 405.2665, found: 405.2670.

2-(di-*tert*-butylphosphaneyl)-1-(2,6-dimethoxyphenyl)-1*H*-imidazole



Chemical Formula:
$C_{19}H_{29}N_2O_2P$
Exact Mass: 348.1967

Obtained as a white solid (112.4 mg, 43% yield) according to the **general procedure B** on 0.75 mmol scale.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.38 (m, 1H), 7.38 – 7.30 (m, 1H), 7.04 – 6.88 (m, 1H), 6.67 – 6.52 (m, 2H), 3.69 (s, 6H), 1.20 (s, 9H), 1.17 (s, 9H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 156.1, 148.4 (d, *J* = 19.0 Hz), 130.2, 129.8, 123.6, 116.5, 103.8, 55.4, 33.2 (d, *J* = 16.2 Hz), 30.3 (d, *J* = 14.4 Hz).

^{31}P NMR (162 MHz, Chloroform-*d*) δ 8.0.

IR (neat): ν (cm^{-1}) 2941, 2895, 1597, 1480, 1300, 1255, 1115, 777, 744, 647.

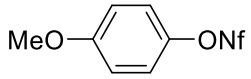
HRMS (ESI): Calcd for $C_{19}H_{30}N_2O_2P$ $[M+H]^+$: 349.2039, found: 349.2041.

Synthesis of nonaflates

General procedure C for synthesis of aryl nonaflates[135]

A slurry of aryl alcohol (1.0 e.q.) in acetonitrile (0.5 M) with potassium carbonate (1.5 e.q.) was stirred vigorously with a magnetic stir bar. Then perfluorobutanesulfonyl fluoride (NfF, 1.2 e.q.) was added in one portion, and the reaction was monitored by GC-MS. Upon completion of the reaction, the inorganic salts were removed by filtration and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography over silica gel.

4-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



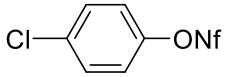
Chemical Formula: $C_{11}H_7F_9O_4S$
Exact Mass: 405.9921

Obtained according to the **general procedure C** as a colorless liquid (99% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.16 (m, 2H), 6.97 – 6.88 (m, 2H), 3.82 (s, 3H).

The NMR data for this compound was consistent with literature data.[135]

4-chlorophenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



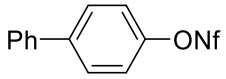
Chemical Formula: $C_{10}H_4ClF_9O_3S$
Exact Mass: 409.9426

Obtained according to the **general procedure C** as a colorless liquid (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.39 (m, 2H), 7.26 – 7.20 (m, 2H).

The NMR data for this compound was consistent with literature data.[135]

[1,1'-biphenyl]-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{16}H_9F_9O_3S$
Exact Mass: 452.0129

Obtained according to the **general procedure C** as a white solid (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 – 7.62 (m, 2H), 7.59 – 7.53 (m, 2H), 7.50 – 7.44 (m, 2H), 7.43 – 7.39 (m, 1H), 7.38 – 7.34 (m, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 149.3, 141.8, 139.5, 129.1, 129.0, 128.2, 127.3, 121.8 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

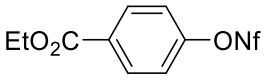
^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.63, -108.87, -120.85, -125.81.

IR (neat): ν (cm^{-1}) 1597, 1485, 1431, 1353, 1197, 1138, 1007, 880, 761, 680.

HRMS (ESI): Calcd for $C_{16}H_9F_9NaO_3S$ $[M+Na]^+$: 475.0021, found: 475.0024.

m.p.: 60-62 °C.

Ethyl 4-(((perfluorobutyl)sulfonyl)oxy)benzoate



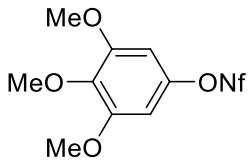
Chemical Formula: $C_{13}H_9F_9O_5S$
Exact Mass: 448.0027

Obtained according to the **general procedure C** as a colorless oil (95% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.20 – 8.09 (m, 2H), 7.39 – 7.29 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

The NMR data for this compound was consistent with literature data.[135]

3,4,5-trimethoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{13}H_{11}F_9O_6S$
Exact Mass: 466.0133

Obtained according to the **general procedure C** as a white solid (95% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.51 – 6.47 (m, 2H), 3.86 (s, 6H), 3.84 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.9, 145.5, 138.0, 99.2, 61.1, 56.5 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

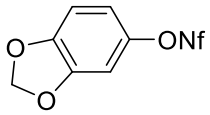
^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.67, -108.93, -120.85, -125.84.

IR (neat): ν (cm^{-1}) 1608, 1503, 1469, 1420, 1354, 1196, 1121, 1033, 970, 856, 795, 732, 698.

HRMS (ESI): Calcd for $C_{13}H_{11}F_9NaO_6S$ $[M+Na]^+$: 489.0025, found: 489.0028**.**

m.p.: 70-72 °C.

benzo[d][1,3]dioxol-5-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{11}H_5F_9O_5S$
Exact Mass: 419.9714

Obtained according to the **general procedure C** as a pale yellow solid (91% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.85 – 6.71 (m, 3H), 6.04 (s, 2H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 147.6, 143.9, 114.6, 108.3, 103.5, 102.6 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

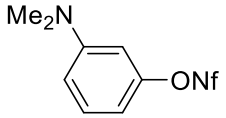
^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.67, -108.90, -120.89, -125.85.

IR (neat): ν (cm^{-1}) 1484, 1420, 1354, 1241, 1189, 1137, 1032, 936, 867, 816, 730, 694, 653.

HRMS (ESI): Calcd for $C_{11}H_5F_9NaO_5S$ $[M+Na]^+$: 442.9606, found: 442.9605.

m.p.: 40-42 °C.

3-(dimethylamino)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{12}H_{10}F_9NO_3S$
Exact Mass: 419.0238

Obtained according to the **general procedure C** as a brown oil (90% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 (t, *J* = 8.3 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.3 Hz, 1H), 6.60 (dd, *J* = 8.1, 2.2 Hz, 1H), 6.53 (t, *J* = 2.4 Hz, 1H), 2.98 (s, 6H).

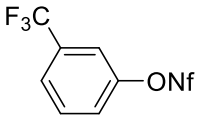
^{13}C NMR (101 MHz, $CDCl_3$) δ 151.9, 151.2, 130.4, 111.8, 108.1, 104.7, 40.4 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.68, -109.17, -120.90, -125.85.

IR (neat): ν (cm^{-1}) 1617, 1568, 1509, 1421, 1354, 1198, 1141, 992, 906, 829, 791, 754, 679.

HRMS (ESI): Calcd for $C_{12}H_{11}F_9NO_3S$ $[M+H]^+$: 420.0310, found: 420.0314.

3-(trifluoromethyl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



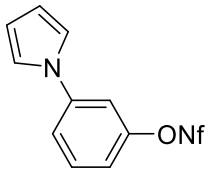
Chemical Formula: $C_{11}H_4F_{12}O_3S$
Exact Mass: 443.9690

Obtained according to the general procedure as a colourless oil (93% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 1H).

The NMR data for this compound was consistent with literature data.[136]

3-(1H-pyrrol-1-yl)phenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{14}H_8F_9NO_3S$
Exact Mass: 441.0081

Obtained according to the **general procedure C** as a yellow oil (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.51 (t, *J* = 8.2 Hz, 1H), 7.43 (ddd, *J* = 8.3, 2.1, 1.0 Hz, 1H), 7.32 (t, *J* = 2.2 Hz, 1H), 7.17 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.09 (t, *J* = 2.2 Hz, 2H), 6.40 (t, *J* = 2.2 Hz, 2H).

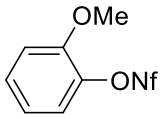
^{13}C NMR (101 MHz, $CDCl_3$) δ 150.4, 142.4, 131.3, 120.0, 119.3, 118.1, 113.6, 111.8 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.66, -108.76, -120.83, -125.81.

IR (neat): ν (cm^{-1}) 1616, 1512, 1419, 1353, 1197, 1141, 1031, 953, 881, 781, 732, 654.

HRMS (ESI): Calcd for $C_{14}H_9F_9NO_3S$ $[M+H]^+$: 442.0154, found: 442.0157.

2-methoxyphenyl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



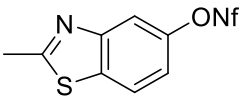
Chemical Formula: $C_{11}H_7F_9O_4S$
Exact Mass: 405.9921

Obtained according to the **general procedure C** as a colourless oil (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (ddd, *J* = 8.2, 7.7, 1.6 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.98 (td, *J* = 7.9, 1.5 Hz, 1H), 3.91 (s, 3H).

The NMR data for this compound was consistent with literature data.[135]

2-methylbenzo[d]thiazol-5-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_{12}H_6F_9NO_3S_2$
Exact Mass: 446.9645

Obtained according to the **general procedure C** as a white solid (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.91 – 7.83 (m, 2H), 7.30 (dd, *J* = 8.8, 2.5 Hz, 1H), 2.86 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 154.1, 148.3, 135.8, 122.6, 118.3, 115.4, 20.5 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

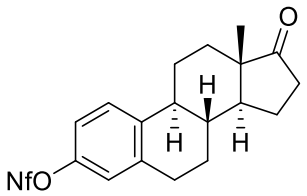
^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.64, -108.66, -120.85, -125.81.

IR (neat): ν (cm^{-1}) 2339, 2192, 2019, 1938, 1521, 1424, 1354, 1199, 1143, 1004, 673.

HRMS (ESI): Calcd for $C_{12}H_7F_9NO_3S_2$ $[M+H]^+$: 447.9718, found: 447.9720.

m.p.: 83-85 °C.

ESTRONE-ONf



Chemical Formula: $C_{22}H_{21}F_9O_4S$
Exact Mass: 552.1017

Obtained according to the **general procedure C** as a white solid (62% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.30 (m, 1H), 7.09 – 7.01 (m, 1H), 7.01 – 6.97 (m, 1H), 2.94 (dd, *J* = 8.7, 4.1 Hz, 2H), 2.51 (dd, *J* = 18.7, 8.8 Hz, 1H), 2.43 – 2.24 (m, 2H), 2.21 – 2.11 (m, 1H), 2.11 – 1.94 (m, 3H), 1.69 – 1.56 (m, 2H), 1.56 – 1.41 (m, 4H), 0.92 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 220.4, 147.9, 140.4, 139.4, 127.3, 121.4, 118.4, 50.5, 48.0, 44.2, 37.9, 35.9, 31.6, 29.5, 26.2, 25.8, 21.7, 13.9 (carbon peaks of nonaflates are omitted due to complicated C-F splitting).

^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.70, -109.15, -120.93, -125.87.

IR (neat): ν (cm^{-1}) 1737, 1490, 1421, 1203, 1144, 1034, 907, 728, 650.

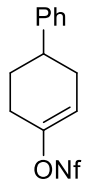
HRMS (ESI): Calcd for $C_{22}H_{21}F_9NaO_4S$ $[M+Na]^+$: 575.0909, found: 575.0916.

m.p.: 55-57 °C.

General procedure D for synthesis of akenyl nonaflates[137]

A solution of *n*-butyllithium in hexane (1.02 e.q.) was added at -78 °C to a solution of *i*Pr_2NH (1.02 e.q.) in THF. After this had remained for 1 h at -78 °C, cyclic ketone (8.0 mmol, 1.0 e.q.) was added, followed by stirring for a further 1 h at -78 °C. Neat NfF (3.02 g, 10.0 mmol) was added dropwise, and the reaction mixture was allowed to warm up to room temperature overnight and then poured into the saturated aq. NH_4Cl. The aqueous phase was extracted with EtOAc, and the combined organic phase was washed consecutively with brine and water, dried over Na_2SO_4. The volatiles were removed *in vacuo* and the residue was subjected to silica gel column chromatography to furnish the desired product.

1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



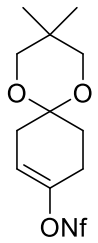
Chemical Formula: $C_{16}H_{13}F_9O_3S$
Exact Mass: 456.0442

Obtained according to the **general procedure D** as a colourless oil (72% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.35 – 7.28 (m, 2H), 7.26 – 7.17 (m, 3H), 5.94 – 5.77 (m, 1H), 2.94 – 2.76 (m, 1H), 2.64 – 2.25 (m, 4H), 2.16 – 2.01 (m, 1H), 2.02 – 1.89 (m, 1H).

The NMR data for this compound was consistent with literature data.[138]

3,3-dimethyl-1,5-dioxaspiro[5.5]undec-8-en-9-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



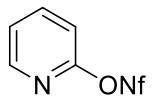
Chemical Formula: $C_{15}H_{17}F_9O_5S$
Exact Mass: 480.0653

Obtained according to the **general procedure D** as a white solid (70% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.61 (t, *J* = 3.8 Hz, 1H), 3.51 (q, *J* = 11.4 Hz, 4H), 2.51 (s, 2H), 2.42 (s, 2H), 2.09 (t, *J* = 6.5 Hz, 2H), 1.01 (s, 3H), 0.93 (s, 3H).

The NMR data for this compound was consistent with literature data.[138]

Pyridin-2-yl 1,1,2,2,3,3,4,4,4-nonafluorobutane-1-sulfonate



Chemical Formula: $C_9H_4F_9NO_3S$
Exact Mass: 376.9768

This nonaflate was prepared according to the procedure reported by Ressig and co-workers.[139]

Pyridin-2-ol (571 mg, 6.0 mmol, 1.0 e.q.) was dissolved in THF (60 mL) and NaH (60%, 720 mg, 18 mmol, 3.00 e.q.) was added under an argon atmosphere. Nonafluorobutanesulfonyl fluoride (NfF, 4.53g, 15 mmol, 2.50 e.q.) was added dropwise at room temperature. The mixture was stirred at room temperature for 7 h, monitored by TLC and GC-MS, and quenched by slow addition of methanol and water. It was extracted with ethylacetate (3 times), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by chromatography on silica gel (cyclohexane/ethyl acetate) to give the corresponding nonaflate derivatives (1.44 g, 64%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.45 – 8.39 (m, 1H), 7.93 – 7.88 (m, 1H), 7.42 – 7.37 (m, 1H), 7.21 – 7.17 (m, 1H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.1, 148.9, 141.1, 124.4, 115.4.

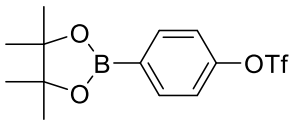
^{19}F NMR (376 MHz, Chloroform-*d*) δ -80.65, -108.99, -120.93, -125.84.

IR (neat): ν (cm^{-1}) 1597, 1424, 1353, 1201, 1141, 1034, 892, 793, 730, 627.

HRMS (ESI): Calcd for $C_9H_5F_9NO_3S$ $[M+H]^+$: 377.9841, found: 377.9845.

Synthesis of triflates

4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl trifluoromethanesulfonate [140]



hemical Formula: $C_{13}H_{16}BF_3O_5S$
Exact Mass: 352.0764

To a flask with magnetic stirring bar was charged 4-BPin phenol (1 equiv, 9.1 mmol, 2.0 g) and *N*-(5-chloropyridin-2-yl)-1,1,1-trifluoro-*N*((trifluoromethyl)sulfonyl)methanesulfonamide (1.1 equiv). The solids were then suspended in CH_2Cl_2 (10 mL/g of phenol). To the reaction was added *i*Pr_2EtN (4 equiv). The reaction was mixed at room temperature, and the progress was monitored by GC-MS. Upon completion of the reaction, the mixture was concentrated, and the resulting residue was purified by flash column chromatography on silica gel using ethyl acetate/cyclohexane (1/10), affording the desired product as a white solid (2.21 g, 69% yield).

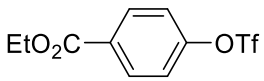
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.94 – 7.85 (m, 2H), 7.30 – 7.23 (m, 2H), 1.35 (s, 12H).

The NMR data for this compound was consistent with literature data.[140, 141]

General procedure E for the synthesis of aryl triflates[110]

A solution of trifluoromethanesulfonic anhydride (1.2 e.q.) in DCM was added dropwise to a solution of pyridine (2.0 e.q.) and phenols (1.0 e.q.) in DCM at 0 °C. After complete addition, the mixture was warmed to R.T. and allowed to stir for 1h. The mixture was diluted with Et_2O, quenched with aq. 10% HCl and washed successively with sat. $NaHCO_3$ and brine. The combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by silica gel column chromatography to give the final product.

Ethyl 4-(((trifluoromethyl)sulfonyl)oxy)benzoate



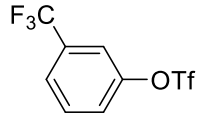
Chemical Formula: $C_{10}H_9F_3O_5S$
Exact Mass: 298.0123

Obtained according to the **general procedure E** as a colourless oil (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.18 – 8.09 (m, 2H), 7.39 – 7.28 (m, 2H), 4.38 (q, *J* = 7.1 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H).

The NMR data for this compound was consistent with literature data.[142]

3-(trifluoromethyl)phenyl trifluoromethanesulfonate



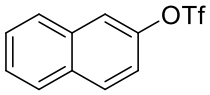
Chemical Formula: $C_8H_4F_6O_3S$
Exact Mass: 293.9785

Obtained according to the **general procedure E** as a colourless oil (81% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.69 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.55 (s, 1H), 7.50 (d, *J* = 8.1 Hz, 1H).

The NMR data for this compound was consistent with literature data.[143]

Naphthalen-2-yl trifluoromethanesulfonate



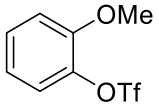
Chemical Formula: $C_{11}H_7F_3O_3S$
Exact Mass: 276.0068

Obtained according to the **general procedure E** as a colourless oil (91% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.93 – 7.84 (m, 3H), 7.79 – 7.74 (m, 1H), 7.61 – 7.55 (m, 2H), 7.43 – 7.36 (m, 1H).

The NMR data for this compound was consistent with literature data.[144]

2-methoxyphenyl trifluoromethanesulfonate



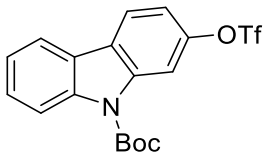
Chemical Formula: $C_8H_7F_3O_4S$
Exact Mass: 256.0017

Obtained according to the **general procedure E** as a colourless oil (98% yield).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 (ddd, *J* = 8.2, 7.7, 1.6 Hz, 1H), 7.22 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.04 (dd, *J* = 8.3, 1.4 Hz, 1H), 6.98 (td, *J* = 7.9, 1.5 Hz, 1H), 3.91 (s, 3H).

The NMR data for this compound was consistent with literature data.[145]

<u>*tert*-butyl 2-(((trifluoromethyl)sulfonyl)oxy)-9H-carbazole-9-carboxylate</u>



Chemical Formula: $C_{18}H_{16}F_3NO_5S$
Exact Mass: 415.0701

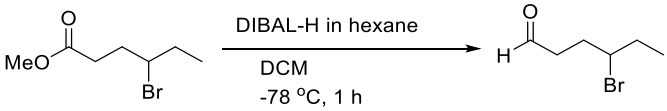
The above triflate was prepared according to the procedure reported by Buchwald and co-workers.[146]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.40 – 8.24 (m, 2H), 8.06 – 7.90 (m, 2H), 7.56 – 7.48 (m, 1H), 7.43 – 7.35 (m, 1H), 7.30 – 7.25 (m, 1H), 1.77 (s, 9H).

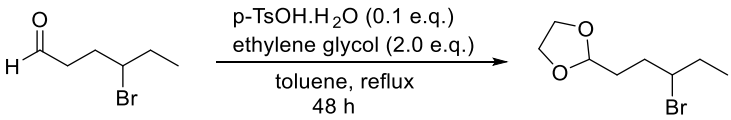
The NMR data for this compound was consistent with literature data.[146]

Synthesis of alkyl bromides

<u>2-(3-bromopentyl)-1,3-dioxolane</u>

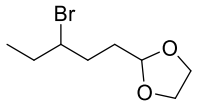


DIBAL-H in Hexane (1.0 M, 1.1 e.q., 41.8 mmol, 41.8 mL) was added dropwise to a solution of methyl 4-bromohexanoate (1.0 e.q., 38 mmol, 7.95 g) in DCM at -78 °C. After being stirred for 1 h at -78 °C, the mixture was poured onto crushed ice and 25 mL of concentrated HCl. The mixture was stirred until it reached 18 °C, and the organic phase was separated, dried and concentrated. The crude product was used directly for the next step.[147]



To a solution of crude aldehyde (38 mmol, 6.8 g) in toluene (100 mL) was added ethylene glycol (76 mmol, 4.72 g) and a catalytic amount of *p*-toluenesulfonic acid monohydrate (3.8

mmol, 0.723 g). The reaction mixture was then stirred at reflux with a Dean-Stark over 48 h. The reaction mixture was cooled to room temperature, quenched by sat. sodium bicarbonate solution and then extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the crude by column chromatography on silica gel (elution from pentane to pentane/Et_2O: 95/5) afforded the desired product (1.88 g, 22% yield over two steps) as a colourless oil.



Chemical Formula: $C_8H_{15}BrO_2$
Exact Mass: 222.0255

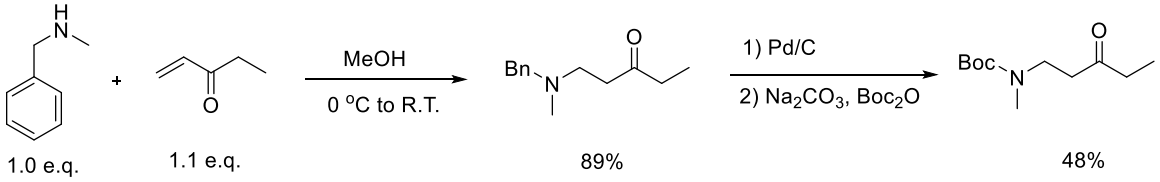
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.87 (t, *J* = 4.2 Hz, 1H), 4.04 – 3.97 (m, 1H), 3.97 – 3.92 (m, 2H), 3.86 – 3.80 (m, 2H), 1.98 – 1.89 (m, 3H), 1.87 – 1.80 (m, 2H), 1.80 – 1.74 (m, 1H), 1.02 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 103.9, 65.0, 65.0, 59.9, 32.9, 32.3, 32.0, 12.1.

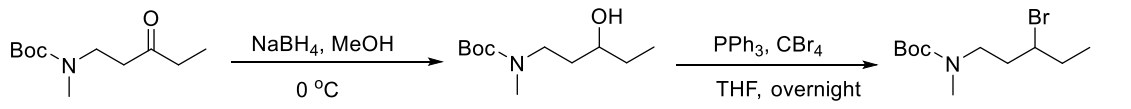
IR (neat): ν (cm^{-1}) 2967, 2294, 2253, 1728, 1633, 1442, 1376, 1038, 919, 749, 665.

***tert*-butyl (3-bromopentyl)(methyl)carbamate**

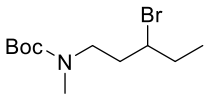
The substrate was prepared according to the procedures for the synthesis of *tert*-butyl (3-bromobutyl)(methyl)carbamate described in *Angew. Chem. Int. Ed.*, 2016, *55*, 14793-14797.



1.0 e.q. 1.1 e.q. 89% 48%



40% over two steps



Chemical Formula: $C_{11}H_{22}BrNO_2$
Exact Mass: 279.0834

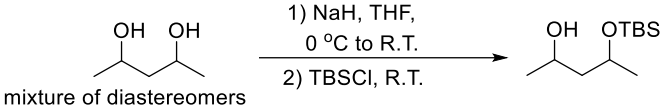
^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.00 – 3.80 (m, 1H), 3.39 – 3.26 (m, 2H), 2.81 (s, 3H), 2.02 – 1.91 (m, 2H), 1.88 – 1.74 (m, 2H), 1.40 (s, 9H), 0.99 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 155.7, 79.5, 56.5, 47.4, 32.5, 32.3, 31.0, 28.5, 12.0.

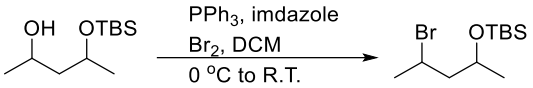
IR (neat): ν (cm^{-1}) 2972, 1694, 1481, 1394, 1226, 1165, 877, 772.

HRMS (ESI): Calcd for $C_{11}H_{22}BrNNaO_2$ $[M+Na]^+$: 302.0726, found: 302.0727.

<u>((4-bromopentan-2-yl)oxy)(*tert*-butyl)dimethylsilane</u>



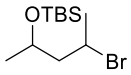
The TBS-protection step was performed according to the procedure reported by Knochel and co-workers.[148]



This compound was prepared according to the procedure reported by Denmark and co-workers.[84]

Bromine (3.19 g, 1.03 mL, 20 mmol, 1.33 equiv) was added dropwise to a stirred suspension of triphenylphosphine (5.23 g, 20 mmol, 1.33 equiv) in CH_2Cl_2 (40 mL) in a round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The flask was then sealed with a rubber septum and purged with argon via an inlet needle. After stirring the resultant pale-yellow suspension for 15 min, a solution of 4-((*tert*-butyldimethylsilyl)oxy)pentan-2-ol (3.28 g, 15 mmol, 1.0 equiv) and imidazole (1.36 g, 20 mmol, 1.33 equiv) in CH_2Cl_2 (20 mL) was added dropwise. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature for 17 h. The mixture was then filtered on celite and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the desired product as a colourless oil (2.95 g, 70%, d.r. 50:50).

The pure diastereoisomer (*syn*- & *anti*-) could be partially separated by silica gel column chromatography (pentane).



Chemical Formula: $C_{11}H_{25}BrOSi$
Exact Mass: 280.0858

The data given below was the mixtures of diastereomers.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.31 – 4.21 (m, 1H), 4.19 – 4.10 (m, 1H), 4.09 – 4.00 (m, 1H), 4.00 – 3.91 (m, 1H), 2.21 – 2.07 (m, 1H), 1.84 – 1.65 (m, 9H), 1.15 (d, *J* = 6.0 Hz, 6H), 0.89 (s, 18H), 0.14 – 0.02 (m, 12H).

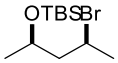
^{13}C NMR (101 MHz, Chloroform-*d*) δ 67.2 (66.9), 51.2 (51.1), 49.5 (47.9), 27.3 (26.5), 26.1 (26.0), 24.3 (23.3), 18.2 (18.2), -4.0 (-4.1), -4.5 (-4.6).

IR (neat): ν (cm^{-1}) 2957, 1462, 1376, 1254, 1146, 1057, 998, 931, 833, 774, 718, 660.

GC-MS (EI) m/z for $C_7H_{16}BrOSi$ ($[M-^tBu]^{+\bullet}$): 223.

The relative configuration was assigned according to the analogies.[148]

(*syn*-4-bromopentan-2-yl)oxy)(*tert*-butyl)dimethylsilane

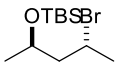


Chemical Formula: $C_{11}H_{25}BrOSi$
Exact Mass: 280.0858

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.27 (ddtd, *J* = 13.4, 10.4, 6.7, 3.5 Hz, 1H), 4.10 – 3.99 (m, 1H), 1.77 (ddd, *J* = 8.2, 6.6, 3.2 Hz, 2H), 1.72 (d, *J* = 6.7 Hz, 3H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.12 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 66.9, 51.2, 49.5, 27.3, 26.1, 24.3, 18.2, -4.0, -4.5.

(*anti*-4-bromopentan-2-yl)oxy)(*tert*-butyl)dimethylsilane

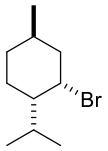


Chemical Formula: $C_{11}H_{25}BrOSi$
Exact Mass: 280.0858

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.20 – 4.09 (m, 1H), 3.97 (h, *J* = 6.1 Hz, 1H), 2.14 (ddd, *J* = 14.3, 7.9, 6.6 Hz, 1H), 1.78 (dt, *J* = 14.0, 6.4 Hz, 1H), 1.72 (d, *J* = 6.6 Hz, 3H), 1.15 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 67.2, 51.1, 47.9, 26.5, 26.0, 23.3, 18.2, -4.1, -4.6.

(±)-2-bromo-1-isopropyl-4-methylcyclohexane



Chemical Formula: $C_{10}H_{19}Br$
Exact Mass: 218.0670

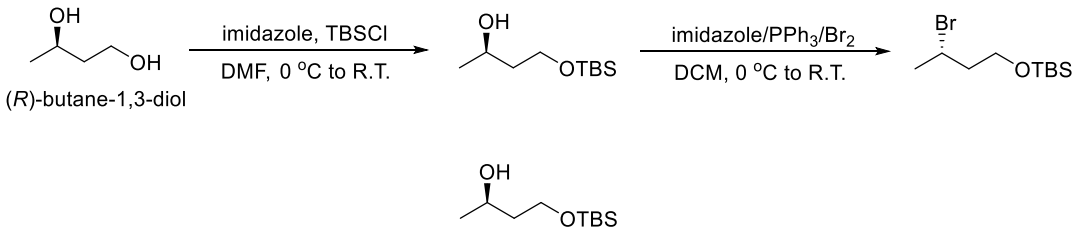
The compound was prepared according to the procedure reported by Atack and co-workers.[149a]

A flame-dried flask equipped with a stir bar was charged with PPh_3 (12.6 g, 48 mmol, 1.2 equiv) and imidazole (3.27 g, 48 mmol, 1.2 equiv) under argon. Anhydrous DCM (200 mL, 0.2 M) was added and the flask was cooled in an ice bath. Bromine (7.67 g, 2.47 mL, 48 mmol, 1.2 equiv) was added dropwise at a rate such that the color dissipates, and the mixture was stirred for 10 minutes. DL-Menthol (6.25 g, 40 mmol, 1 equiv), diluted in 25 mL DCM, was added dropwise at 0 °C, and the reaction mixture was stirred at 0 °C for 1 hour. After one hour, the reaction was allowed to warm to room temperature and stirred for an additional 12 hours. The reaction was concentrated under reduced pressure and diluted with hexanes:EtOAc (4:1) and filtered through a plug of silica. Filtrate was concentrated under reduced pressure and purified by silica flash chromatography to yield the desired product as a colorless liquid (3.5 g, 40%).

^{1}H NMR (500 MHz, Chloroform-*d*) δ 4.74 – 4.60 (m, 1H), 2.21 – 2.13 (m, 1H), 2.02 – 1.91 (m, 1H), 1.80 – 1.71 (m, 2H), 1.53 – 1.31 (m, 3H), 0.93 (d, *J* = 1.1 Hz, 3H), 0.92 (d, *J* = 1.2 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.82 – 0.74 (m, 1H).

The NMR data for this compound was consistent with literature data.[149b]

(*S*)-(3-bromobutoxy)(*tert*-butyl)dimethylsilane

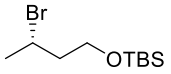


Chemical Formula: $C_{10}H_{24}O_2Si$
Exact Mass: 204.1546

(*R*)-butane-1,3-diol (1.0 g, 11.1 mmol, 1.0 e.q., from Fluorochem) and imidazole (1.66 g, 24.4 mmol, 2.2 e.q.) were stirred in DMF (7.5 mL) for 1 h at 0 ºC. TBSCl (1.67 g, 11.1 mmol, 1.0 e.q.) were then added to the mixture, which was then allowed to warm to room temperature and stirred for 18 h. The mixture was quenched with water and extracted with Et_2O (three times). The combined organic phases were then washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give the desired product as a colourless oil (1.94 g, 85%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.10 – 3.96 (m, 1H), 3.92 – 3.75 (m, 2H), 3.43 (brs, 1H), 1.73 – 1.53 (m, 2H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 6H).

The NMR data for this compound was consistent with literature data.[150]



Chemical Formula: $C_{10}H_{23}BrOSi$
Exact Mass: 266.0702

This compound was prepared according to the procedure reported by Denmark and co-workers.[84]

Bromine (1.78 g, 0.57 mL, 11.2 mmol, 1.2 equiv) was added dropwise via syringe to a stirred suspension of triphenylphosphine (2.93 g, 11.2 mmol, 1.2 equiv) in CH_2Cl_2 (25 mL) in a round-bottomed flask equipped with a stirrer bar and cooled in an ice/water bath (open to air). The ask was then sealed with a rubber septum and purged with argon. After stirring the resultant pale-yellow suspension for 15 min, a solution of (*R*)-4-((*tert*-butyldimethylsilyl)oxy)butan-2-ol (1.9 g, 9.3 mmol, 1.0 equiv) and imidazole (0.76 g, 11.2 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) was added via cannula over ca. 5 min. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature over 17 h. The mixture was then filtered through a sintered funnel under house vacuum and carefully concentrated *in vacuo* to leave a yellow oil residue (i.e., avoiding precipitating the phosphorus-containing residues at this point). A stirrer bar was added to the residue and rapid stirring was commenced. Cycolohexane (30 mL) was quickly added in one portion to precipitate the phosphorus-containing residues as a white solid. The mixture was rinsed through a pad of SiO_2 using cyclohexane (3 × 15 mL) and the filtrate was concentrated *in vacuo* to give a clear, colorless oil. Purication by silica gel column chromatography gave (*S*)-product as a clear, colorless oil (731 mg, 29%).

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.39 – 4.24 (m, 1H), 3.75 (t, *J* = 5.8 Hz, 2H), 2.00 – 1.93 (m, 2H), 1.74 (d, *J* = 6.7 Hz, 3H), 0.89 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H).

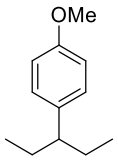
^{13}C NMR (126 MHz, Chloroform-*d*) δ 61.1, 48.5, 44.0, 26.8, 26.1, 18.5, -5.2.

GC-MS (EI) m/z for $C_6H_{14}BrOSi$ ($[M-^tBu]^{+\bullet}$): 209.

General procedure F for the direct Barbier-Negishi couplings of secondary alkyl bromides

An oven-dried 10.0 – 20.0 mL Biotage microwave vial equipped with a stirring bar was taken into the glovebox, magnesium powder (1.5 e.q.), lithium chloride (1.5 e.q.), zinc chloride (2.0 e.q.), Pd_2dba_3 (97%) (2.5 mol%) and **L^{13}** (5.0 mol%) were added to the vial. The vial was capped with a Biotage cap using a crimper and removed from the glovebox. Then, a solution of sulfonates (1.0 mmol, 1.0 e.q.) and alkyl bromides (1.5 e.q.) in THF (5.0 mL, 0.2 M) was added to the mixture via syringe under argon atmosphere. The vial was wrapped with tape and placed into a 25 ^oC water bath. The reaction mixture was stirred at that temperature for 24 h. After that time, the reaction mixture was diluted with Et_2O (5.0 mL) and carefully quenched with saturated NH_4Cl solution (5.0 mL) (An aliquot of the crude mixture was measured by GC or GC-MS to determine the ratio of direct coupling product and migrative coupling product). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 X 5.0 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography gave the desired product as a mixture of direct/migrative coupling products (which could not be separated by column chromatgraphy).

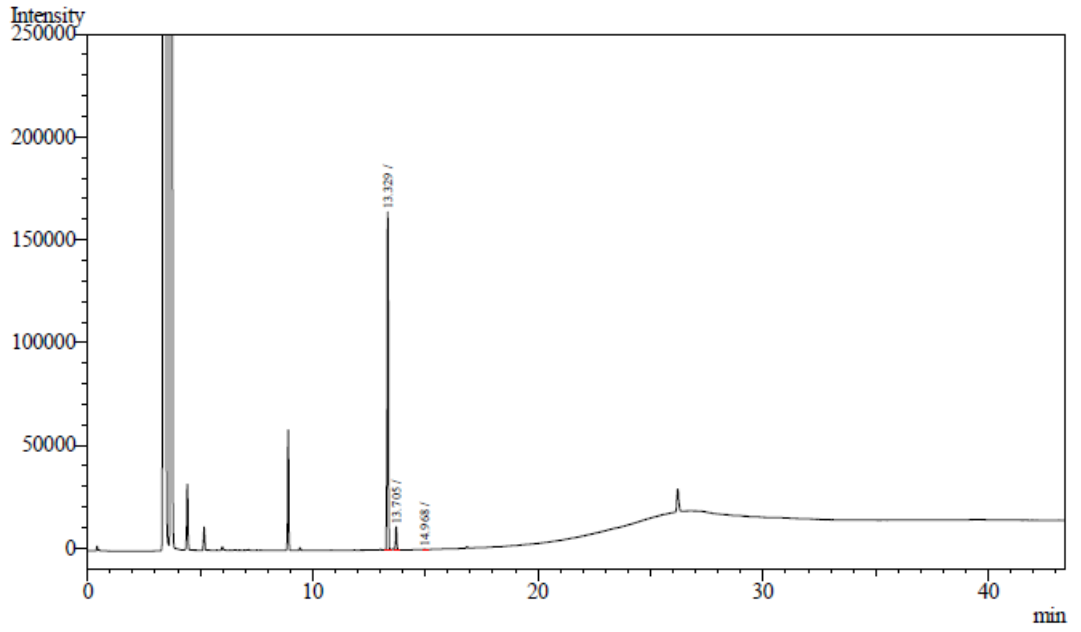
1-methoxy-4-(pentan-3-yl)benzene 3-10a

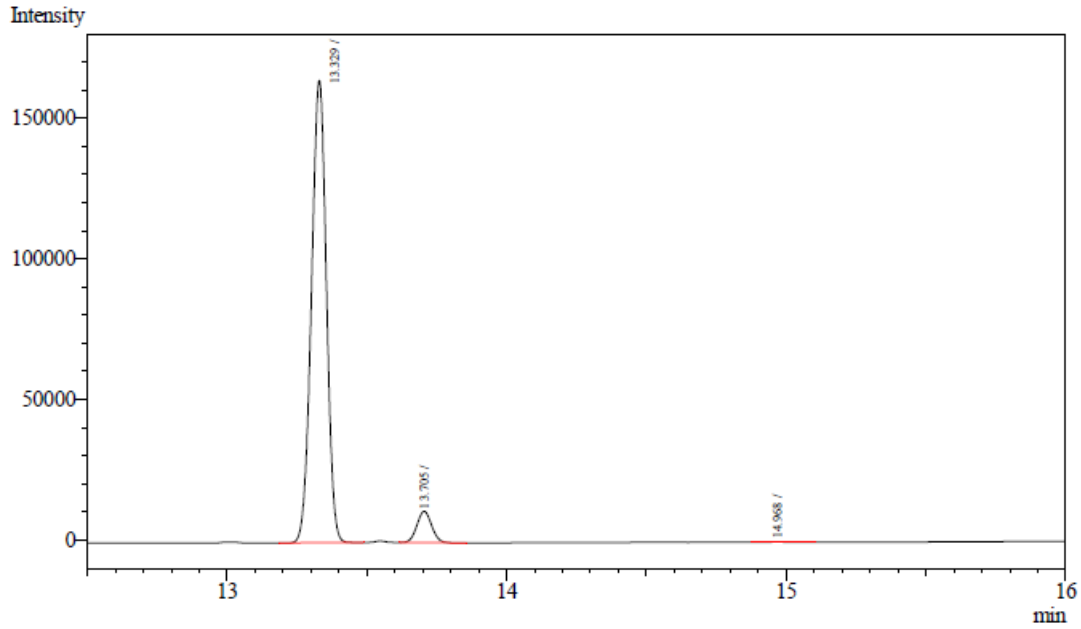


Chemical Formula: $C_{12}H_{18}O$
Exact Mass: 178.1358

Obtained as the mixture of cross-coupling products (160 mg colourless oil, 90% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





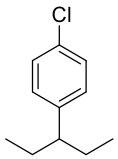
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	13.329	609734	163710	93.655	93.6547
2	13.705	40625	11115	6.240	6.2400
3	14.968	686	186	0.105	0.1054
Total		651045	175011	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.03 (m, 2H), 6.91 – 6.81 (m, 2H), 3.81 (s, 3H), 2.36 – 2.19 (m, 1H), 1.76 – 1.61 (m, 2H), 1.57 – 1.47 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.8, 138.0, 128.7, 113.6, 55.3, 49.0, 29.6, 12.3.

The NMR data for this compound was consistent with literature datas.[151]

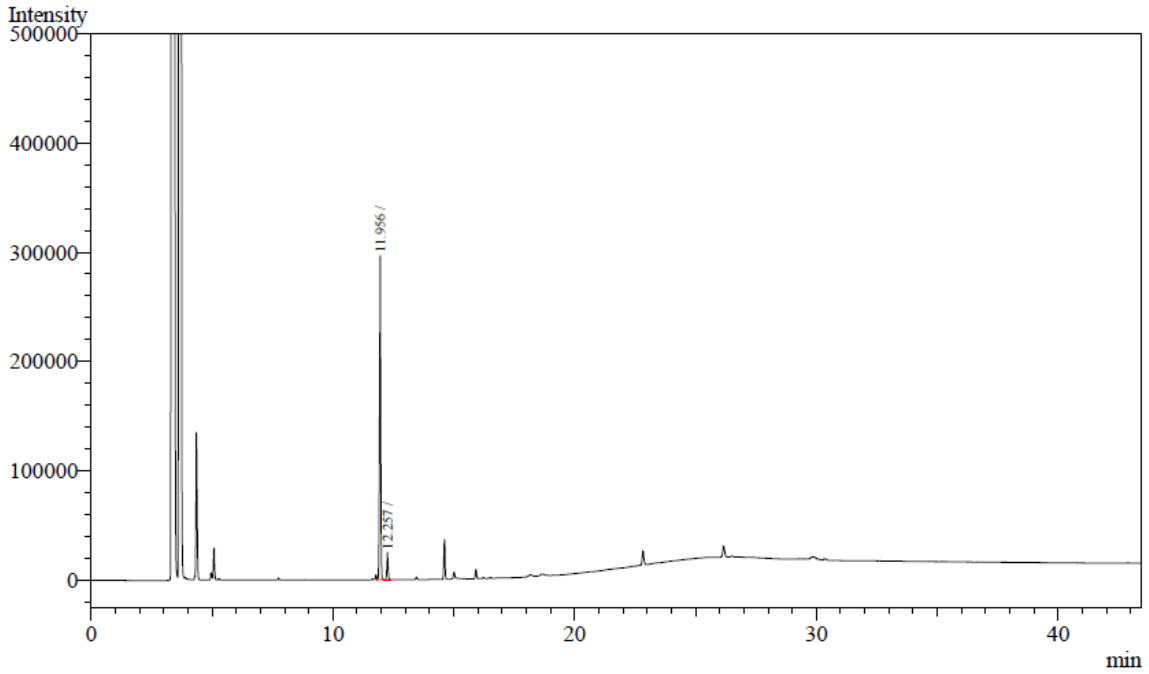
1-chloro-4-(pentan-3-yl)benzene 3-10b

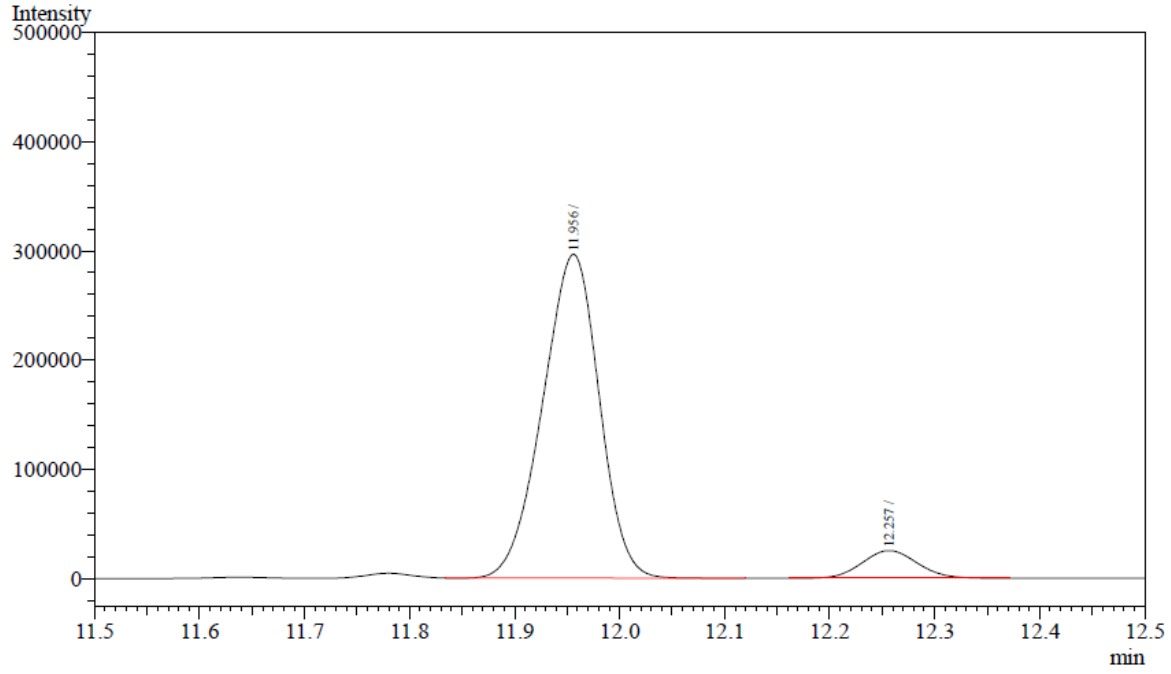


Chemical Formula: $C_{11}H_{15}Cl$
Exact Mass: 182.0862

Obtained as the mixture of cross-coupling products (135 mg colourless oil, 74% yield, 92:8) according to the **general procedure F**.

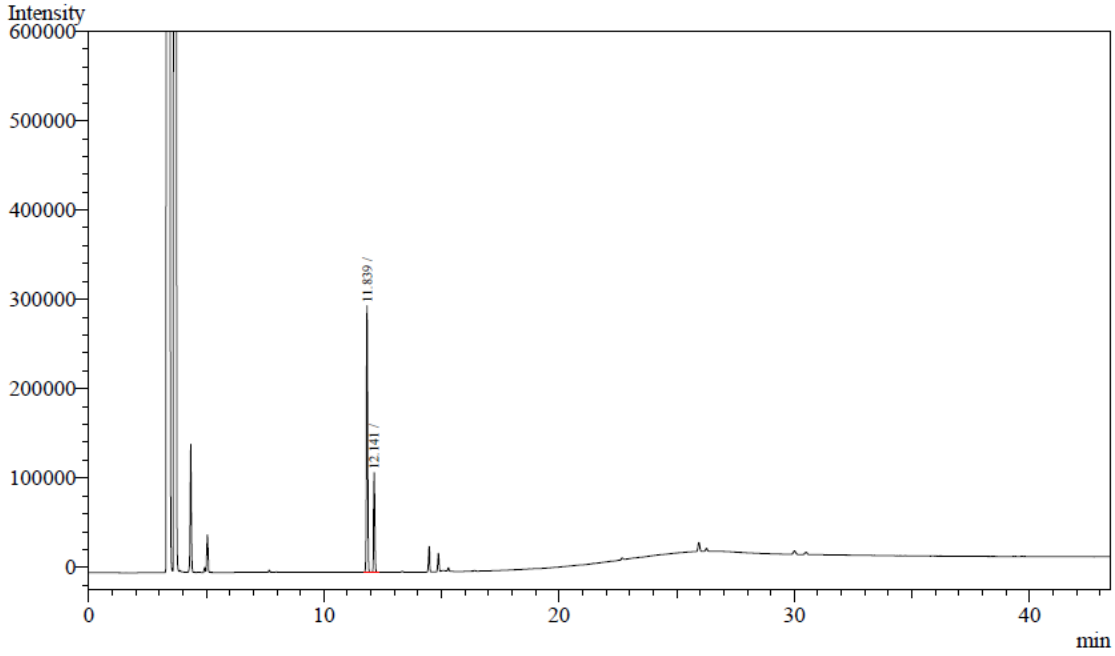
GC trace of the crude mixture with L^{13} as the ligand

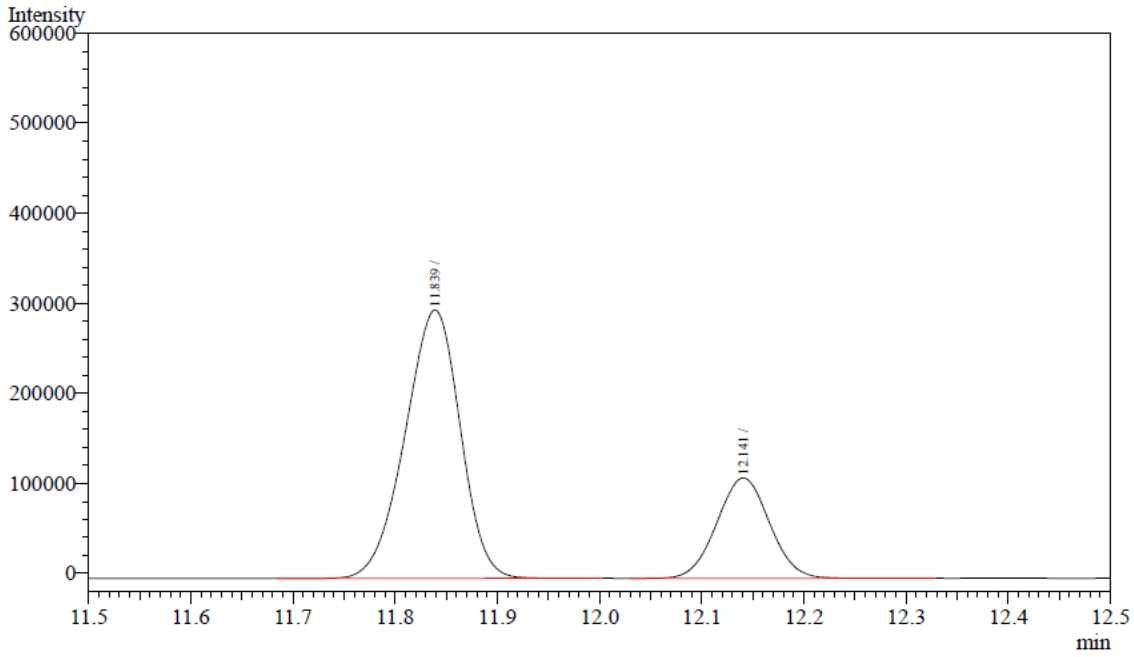




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	11.956	1110494	294697	92.325	92.3248
2	12.257	92318	25226	7.675	7.6752
Total		1202812	319923	100.000	100.0000

GC trace of the crude mixture with CPhos as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	11.839	1118569	297076	73.637	73.6372
2	12.141	400458	111365	26.363	26.3628
Total		1519027	408441	100.000	100.0000

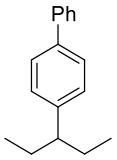
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.44 – 7.16 (m, 2H), 7.09 – 7.01 (m, 2H), 2.33 – 2.23 (m, 1H), 1.75 – 1.60 (m, 2H), 1.57 – 1.46 (m, 2H), 0.75 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 144.4, 131.5, 129.3, 128.4, 49.3, 29.4, 12.2.

IR (neat): ν (cm^{-1}) 2962, 2927, 2874, 1493, 1091, 823.

GC-MS (EI) m/z for $C_{11}H_{15}Cl$ ($[M]^{+\bullet}$): 182.

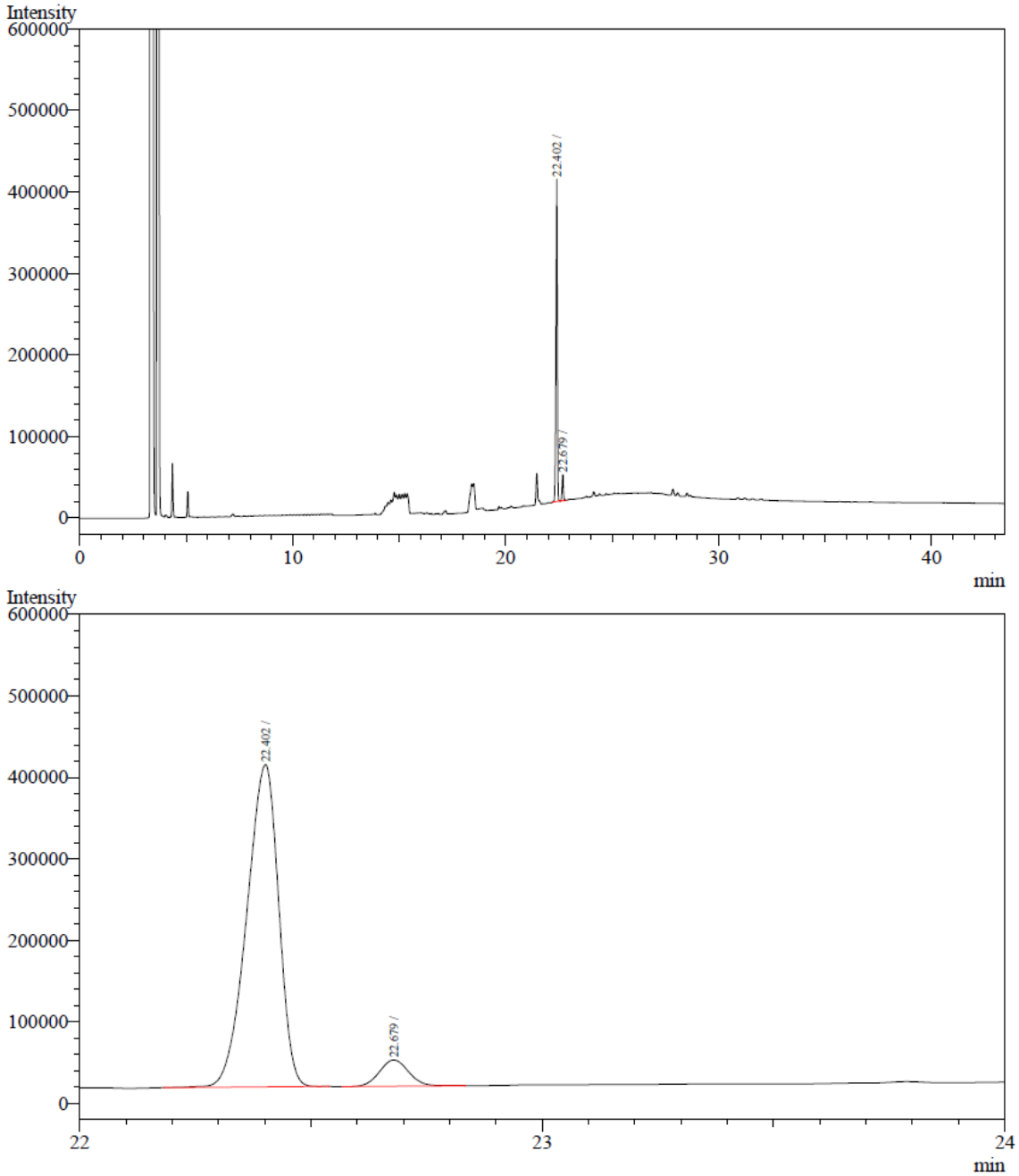
4-(pentan-3-yl)-1,1'-biphenyl 3-10c



Chemical Formula: $C_{17}H_{20}$
Exact Mass: 224.1565

Obtained as the mixture of cross-coupling products (192 mg white solid, 86% yield, 93:7) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	22.402	1896742	394565	93.086	93.0858
2	22.679	140885	32030	6.914	6.9142
Total		2037627	426595	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.63 – 7.58 (m, 2H), 7.55 – 7.51 (m, 2H), 7.46 – 7.40 (m, 2H), 7.35 – 7.30 (m, 1H), 7.24 – 7.19 (m, 2H), 2.45 – 2.31 (m, 1H), 1.79 – 1.67 (m, 2H), 1.64 – 1.55 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 6H).

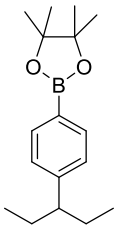
^{13}C NMR (101 MHz, $CDCl_3$) δ 145.1, 141.3, 138.7, 128.8, 128.3, 127.1, 127.0, 127.0, 49.5, 29.4, 12.4.

IR (neat): ν (cm^{-1}) 2961, 2920, 2869, 1599, 1456, 1004, 833, 758, 689.

GC-MS (EI) m/z for $C_{17}H_{20}$ ($[M]^{+\bullet}$): 224.

m.p.: 57-59 ^{o}C.

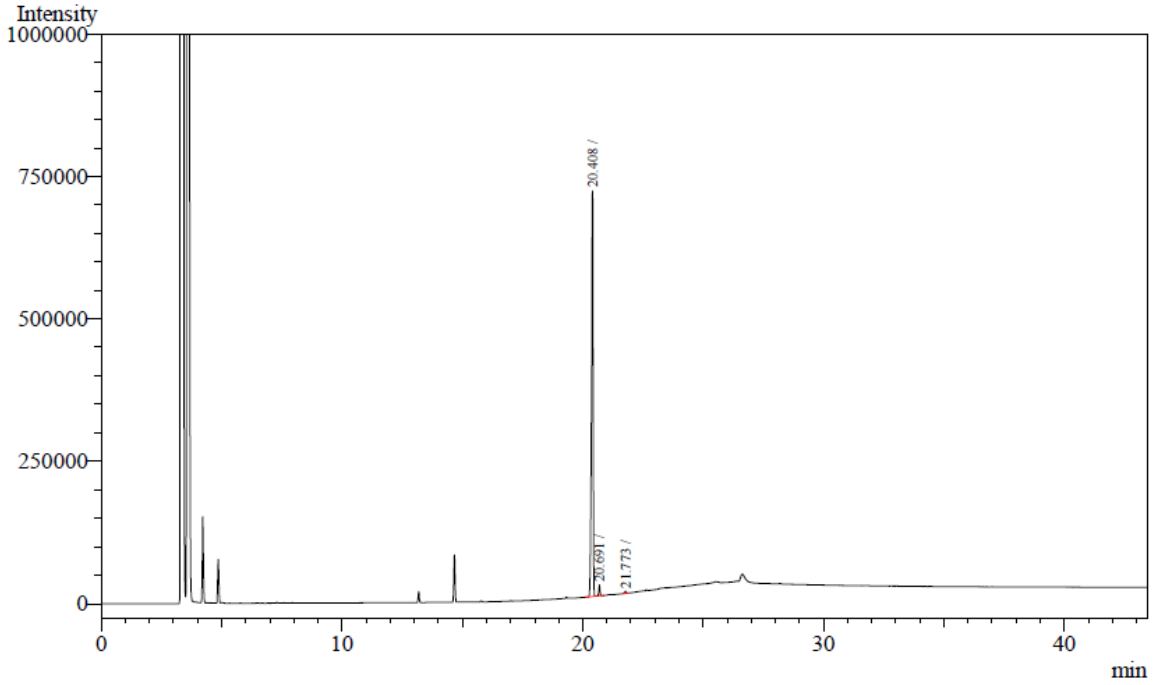
4,4,5,5-tetramethyl-2-(4-(pentan-3-yl)phenyl)-1,3,2-dioxaborolane 3-10d

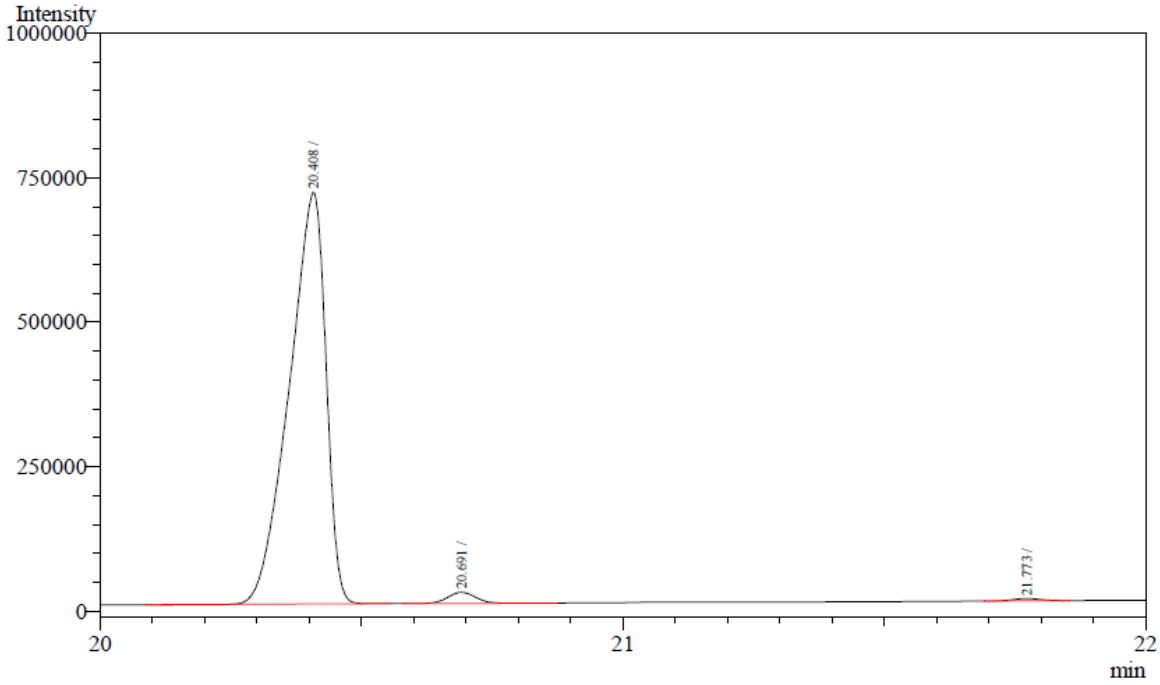


Chemical Formula: $C_{17}H_{27}BO_2$
Exact Mass: 274.2104

Obtained as the mixture of cross-coupling products (176 mg white solid, 64% yield, 98:2) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.408	3464211	709775	97.598	97.5982
2	20.691	70982	19088	2.000	1.9998
3	21.773	14268	3722	0.402	0.4020
Total		3549461	732585	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.79 – 7.70 (m, 2H), 7.19 – 7.11 (m, 2H), 2.40 – 2.26 (m, 1H), 1.75 – 1.63 (m, 2H), 1.60 – 1.50 (m, 2H), 1.34 (s, 12H), 0.76 (t, *J* = 7.4 Hz, 6H).

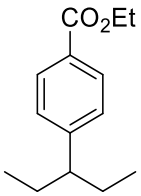
^{13}C NMR (101 MHz, $CDCl_3$) δ 149.5, 134.9, 127.5, 83.7, 50.1, 29.3, 25.0, 12.3.

IR (neat): ν (cm^{-1}) 2968, 2928, 1610, 1460, 1357, 1271, 1140, 1089, 1016, 962, 835, 748, 660.

HRMS (ESI): Calcd for $C_{17}H_{27}BNaO_2$ $[M+Na]^+$: 297.1999, found: 297.2001.

m.p.: 88-90 °C.

ethyl 4-(pentan-3-yl)benzoate 3-10e



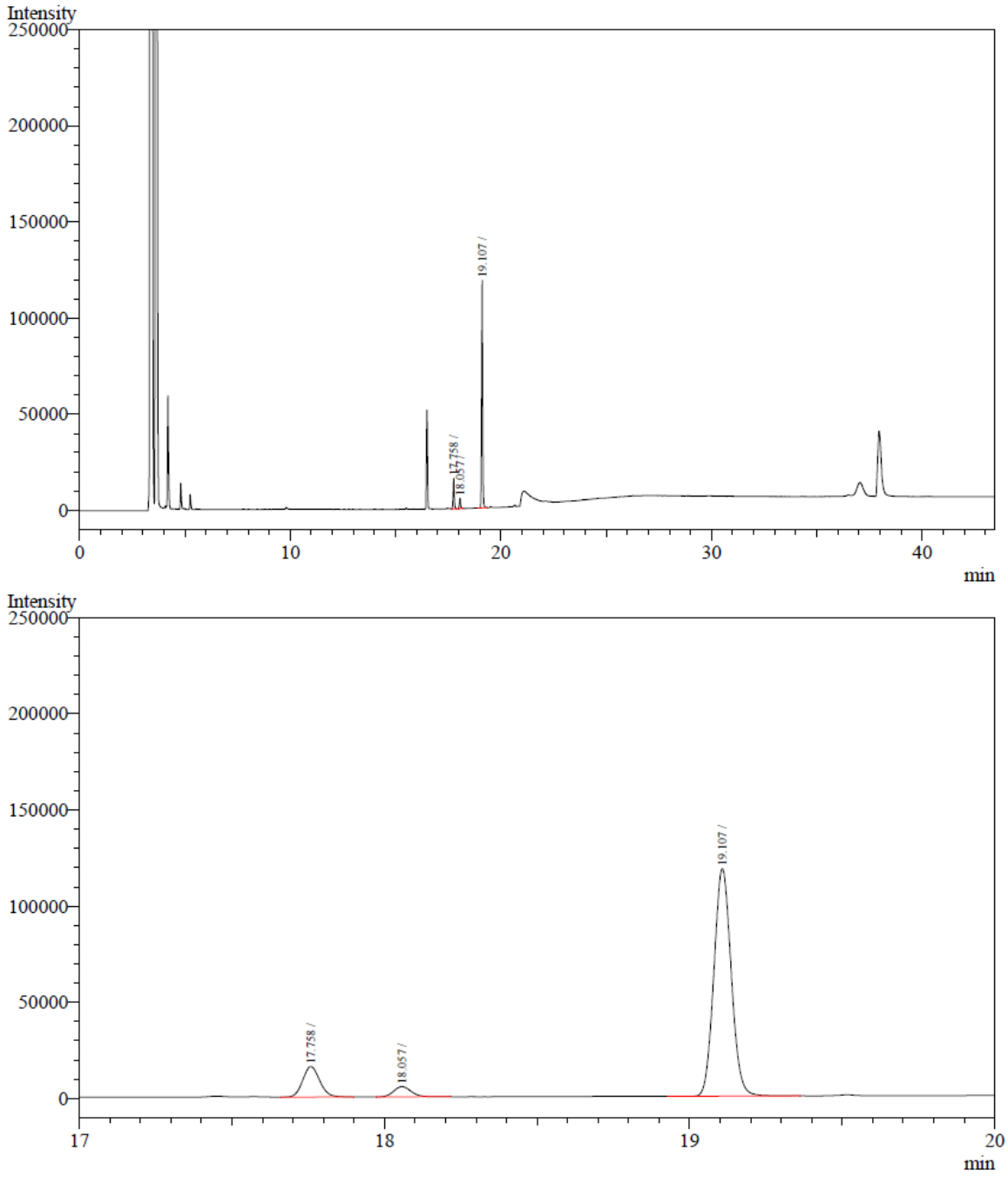
Chemical Formula: $C_{14}H_{20}O_2$
Exact Mass: 220.1463

Obtained as the mixture of cross-coupling products according to the **general procedure F**.

From ONf: 33 mg colourless oil, 15% yield, 10:90.

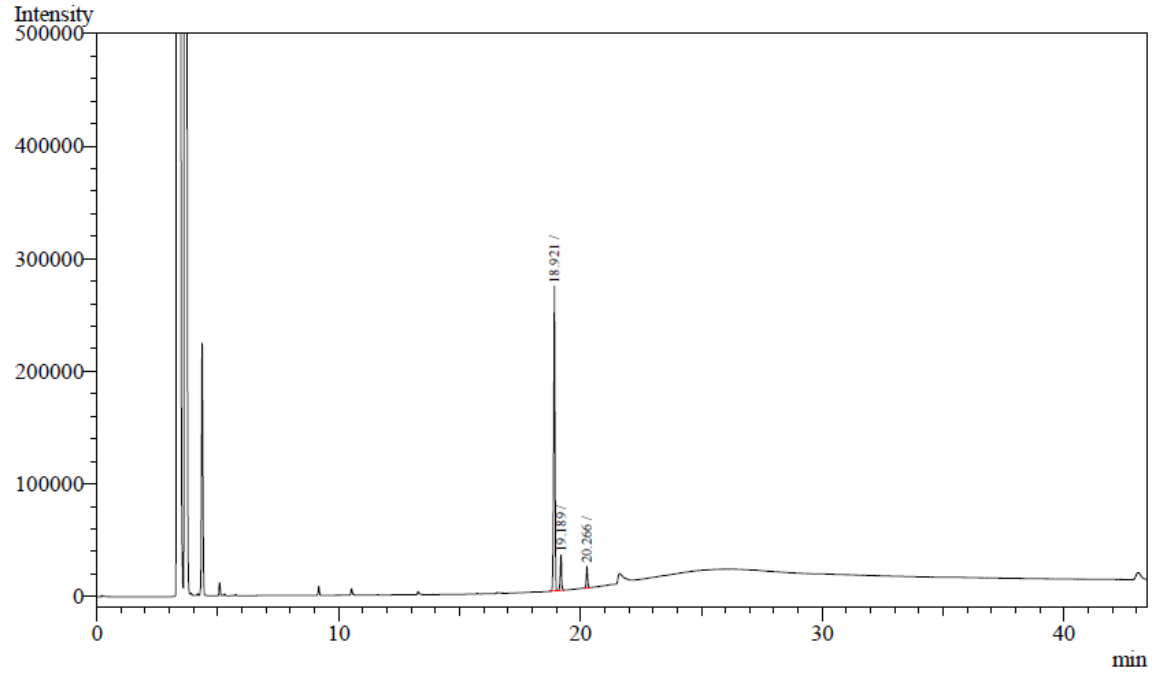
From OTf: 163 mg colourless oil, 74% yield, 85:15.

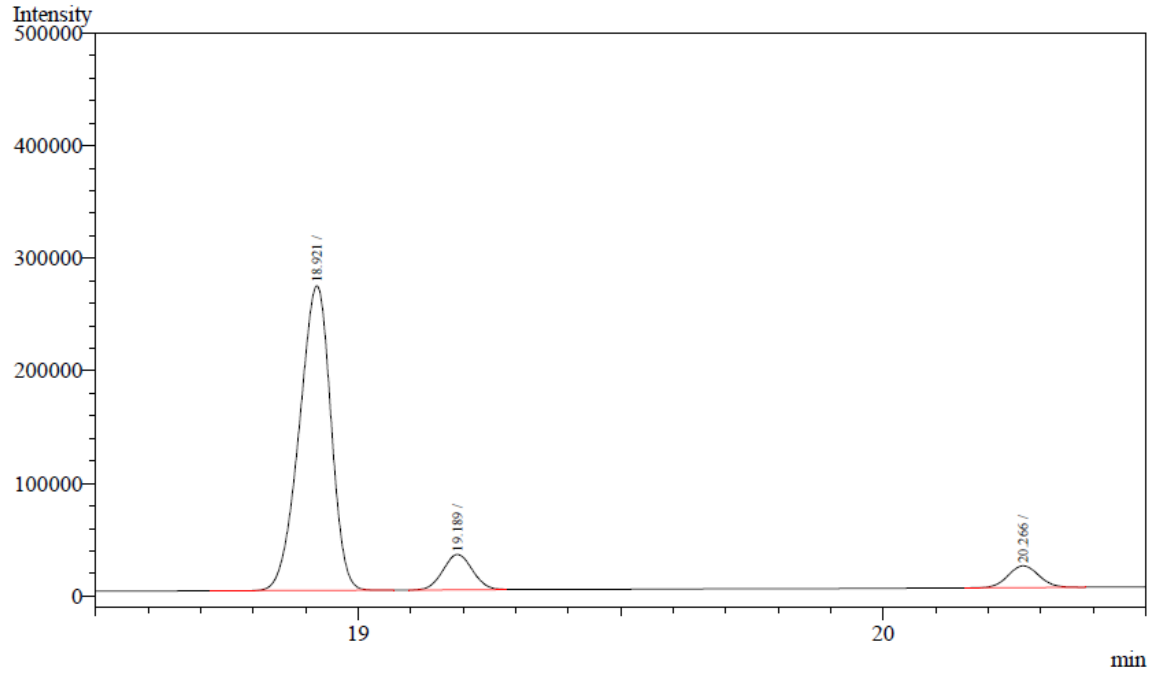
GC trace of the crude mixture using nonaflate as the substrate and L^{13} as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	17.758	60849	15769	11.081	11.0805
2	18.057	21185	5295	3.858	3.8578
3	19.107	467120	118094	85.062	85.0617
Total		549154	139158	100.000	100.0000

GC trace of the crude mixture using triflate as the substrate and L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	18.921	1131935	270220	84.971	84.9708
2	19.189	122026	31280	9.160	9.1601
3	20.266	78186	19226	5.869	5.8691
Total		1332147	320726	100.000	100.0000

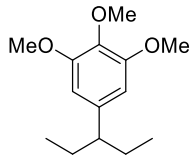
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.99 – 7.94 (m, 2H), 7.23 – 7.15 (m, 2H), 4.36 (q, *J* = 7.1 Hz, 2H), 2.45 – 2.33 (m, 1H), 1.77 – 1.66 (m, 2H), 1.59 – 1.52 (m, 2H), 1.39 (t, *J* = 7.1 Hz, 3H), 0.76 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 166.9, 151.5, 129.6, 127.9, 127.1, 60.8, 49.9, 29.3, 14.5, 12.2.

IR (neat): ν (cm^{-1}) 2963, 1719, 1610, 1461, 1367, 1275, 1179, 1105, 1022, 853, 766, 708.

HRMS (ESI): Calcd for $C_{14}H_{20}NaO_2$ $[M+Na]^+$: 243.1356, found: 243.1355.

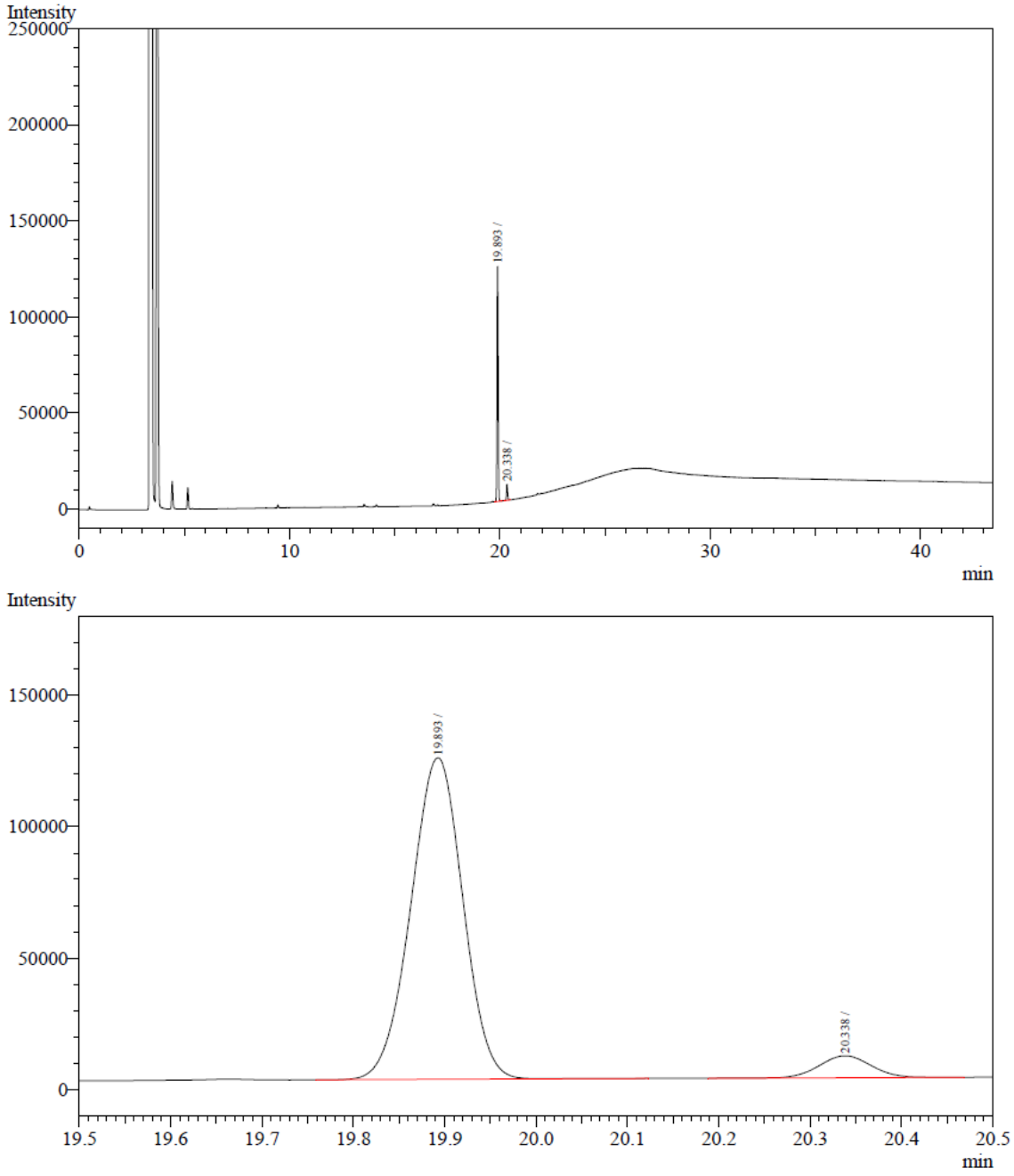
1,2,3-trimethoxy-5-(pentan-3-yl)benzene 3-10f



Chemical Formula: $C_{14}H_{22}O_3$
Exact Mass: 238.1569

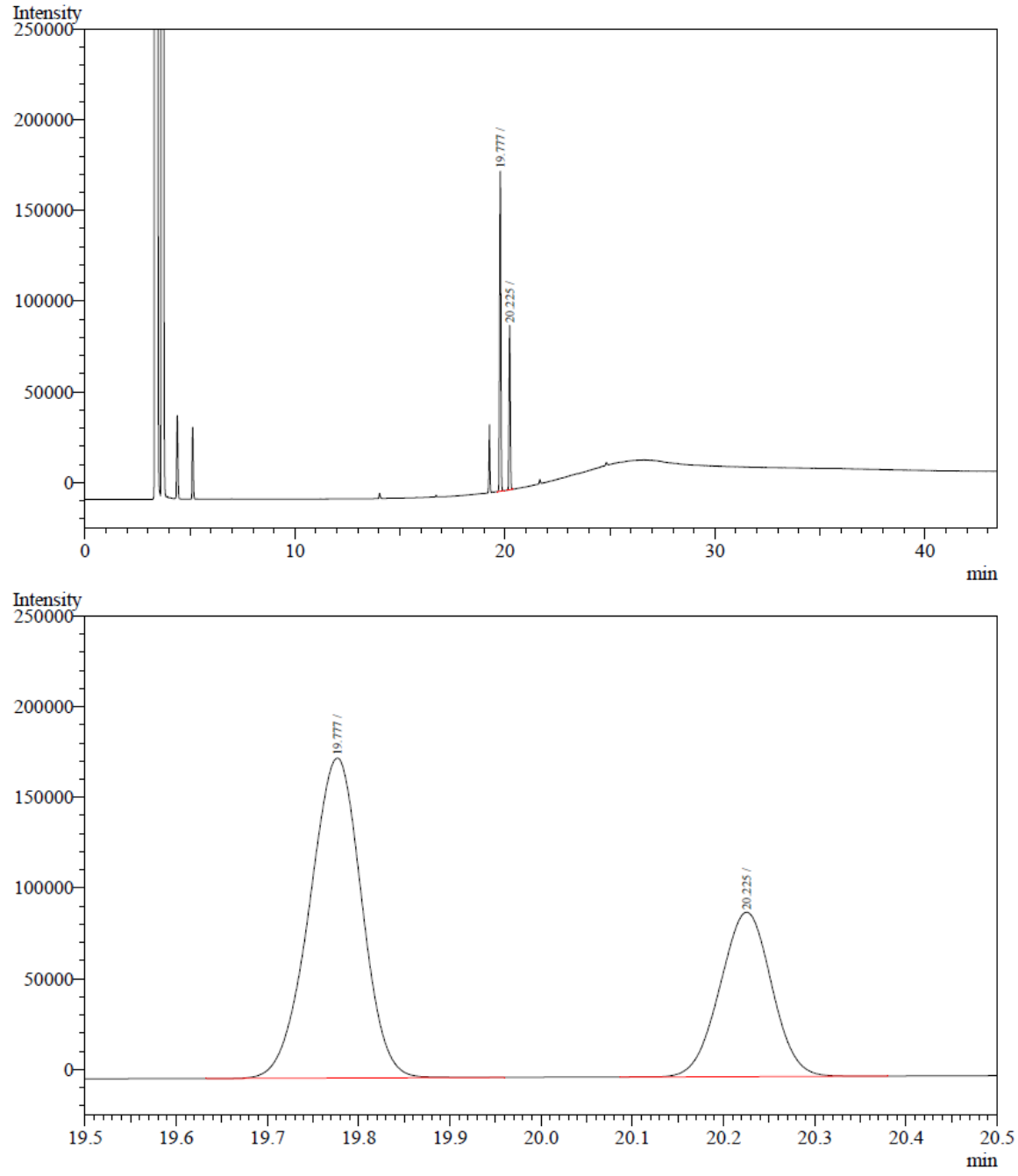
Obtained as the mixture of cross-coupling products (219 mg colourless oil, 92% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	19.893	484581	122169	93.629	93.6290
2	20.338	32973	8289	6.371	6.3710
Total		517554	130458	100.000	100.0000

GC trace of the crude mixture with CPhos as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	19.777	701683	176126	66.296	66.2962
2	20.225	356723	90345	33.704	33.7038
Total		1058406	266471	100.000	100.0000

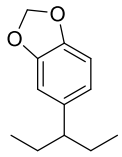
^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.36 – 6.32 (m, 2H), 3.85 (s, 6H), 3.83 (s, 3H), 2.29 – 2.17 (m, 1H), 1.73 – 1.60 (m, 2H), 1.56 – 1.47 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 153.1, 141.9, 136.2, 104.7, 61.0, 56.2, 50.3, 29.5, 12.4.

IR (neat): ν (cm^{-1}) 2930, 1588, 1509, 1456, 1319, 1233, 1123, 1011, 826, 771, 662.

HRMS (ESI): Calcd for $C_{14}H_{22}NaO_3$ $[M+Na]^+$: 261.1461, found: 261.1464.

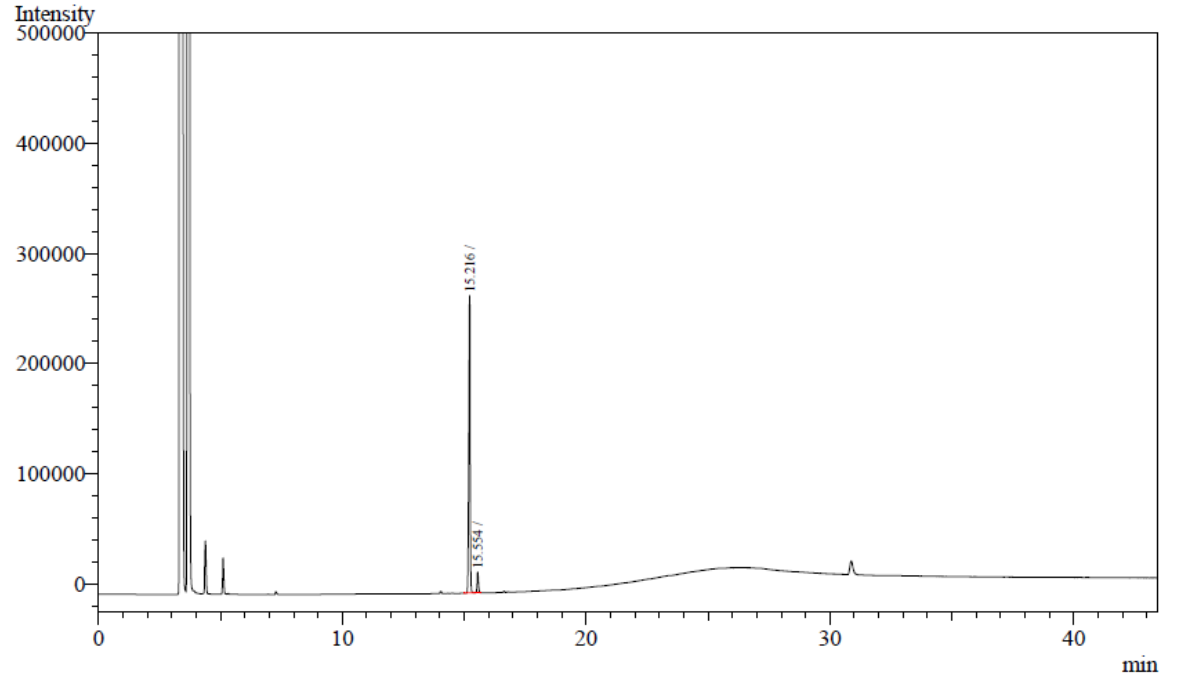
5-(pentan-3-yl)benzo[d][1,3]dioxole 3-10g

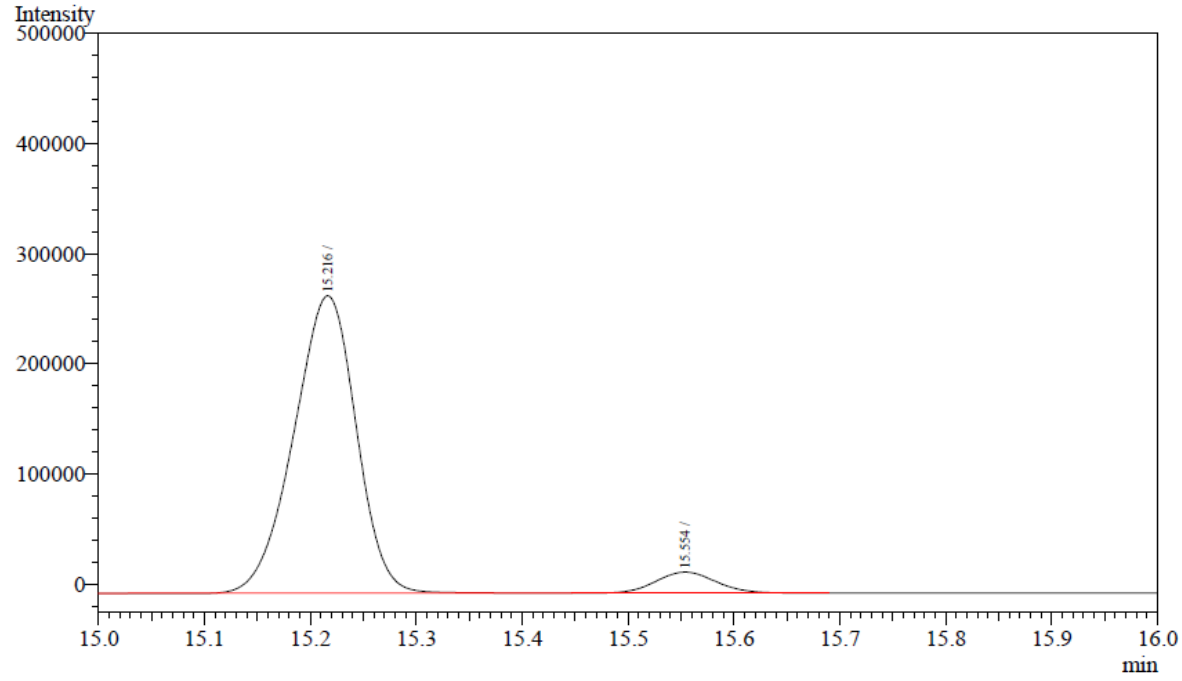


Chemical Formula: $C_{12}H_{16}O_2$
Exact Mass: 192.1150

Obtained as the mixture of cross-coupling products (155 mg colourless oil, 81% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





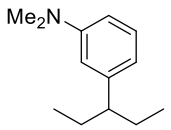
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	15.216	1104981	269369	93.671	93.6708
2	15.554	74662	18819	6.329	6.3292
Total		1179643	288188	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.73 (d, *J* = 7.9 Hz, 1H), 6.64 (d, *J* = 1.7 Hz, 1H), 6.58 (dd, *J* = 7.9, 1.7 Hz, 1H), 5.92 (s, 2H), 2.31 – 2.18 (m, 1H), 1.71 – 1.59 (m, 2H), 1.53 – 1.42 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.7, 145.6, 139.9, 121.1, 108.0, 107.8, 100.8, 49.6, 29.6, 12.3.

The NMR data for this compound was consistent with literature data.[39c]

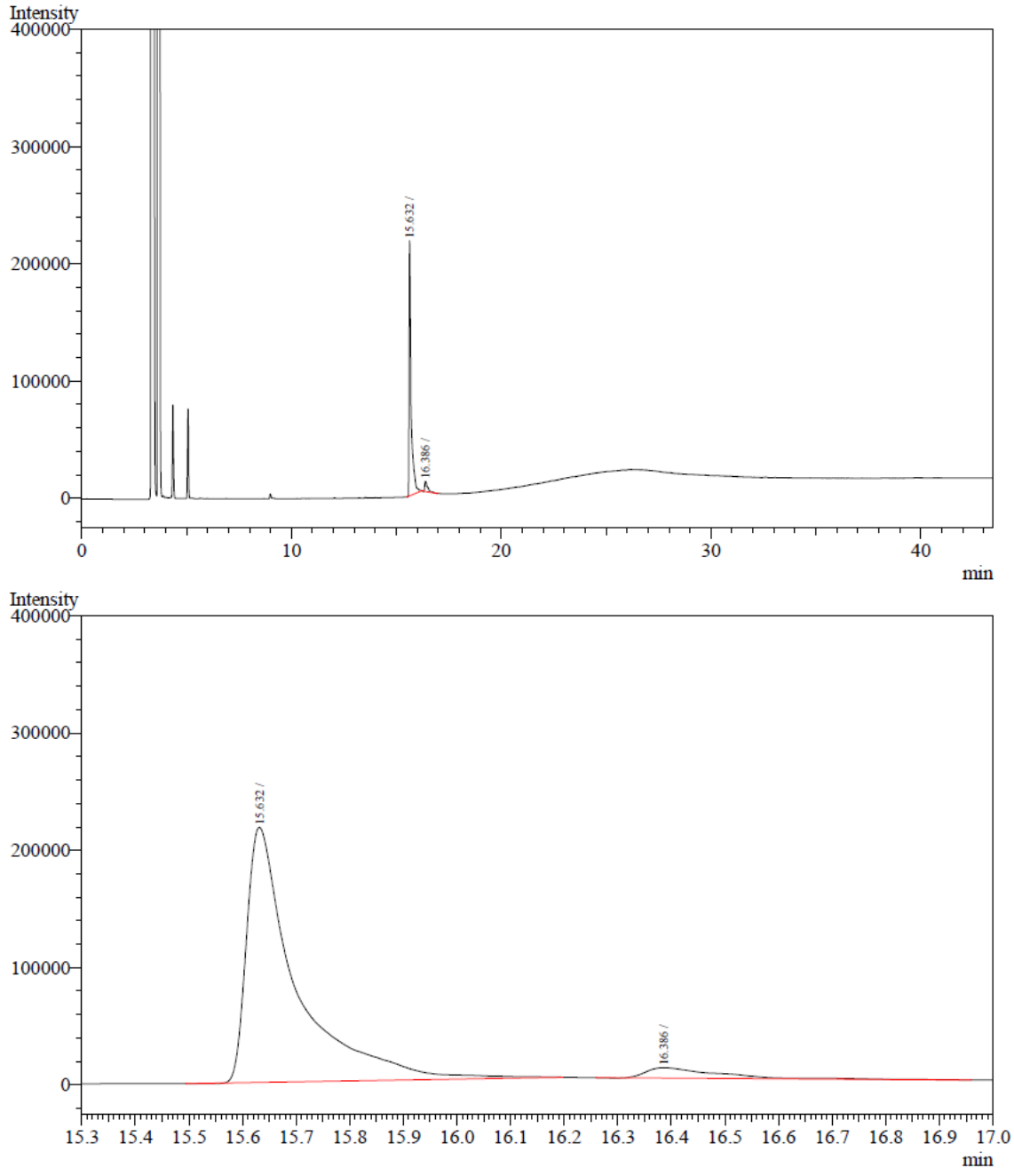
<u>*N*, *N*-dimethyl-3-(pentan-3-yl)aniline 3-10h</u>



Chemical Formula: $C_{13}H_{21}N$
Exact Mass: 191.1674

Obtained as the mixture of cross-coupling products (160 mg colourless oil, 84% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L[13] as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	15.632	1401894	217227	94.396	94.3955
2	16.386	83234	8844	5.604	5.6045
Total		1485128	226071	100.000	100.0000

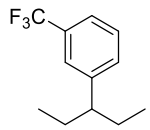
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.18 (t, *J* = 8.1 Hz, 1H), 6.64 – 6.51 (m, 3H), 2.95 (s, 6H), 2.32 – 2.22 (m, 1H), 1.75 – 1.63 (m, 2H), 1.62 – 1.51 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 150.7, 146.9, 128.8, 116.5, 112.8, 110.4, 50.3, 40.9, 29.4, 12.5.

IR (neat): ν (cm^{-1}) 2959, 2924, 2871, 1601, 1499, 1457, 1346, 1229, 1158, 1061, 995, 846, 770, 698.

HRMS (ESI): Calcd for $C_{13}H_{22}N$ $[M+H]^+$: 192.1747, found: 192.1746.

1-(pentan-3-yl)-3-(trifluoromethyl)benzene 3-10i



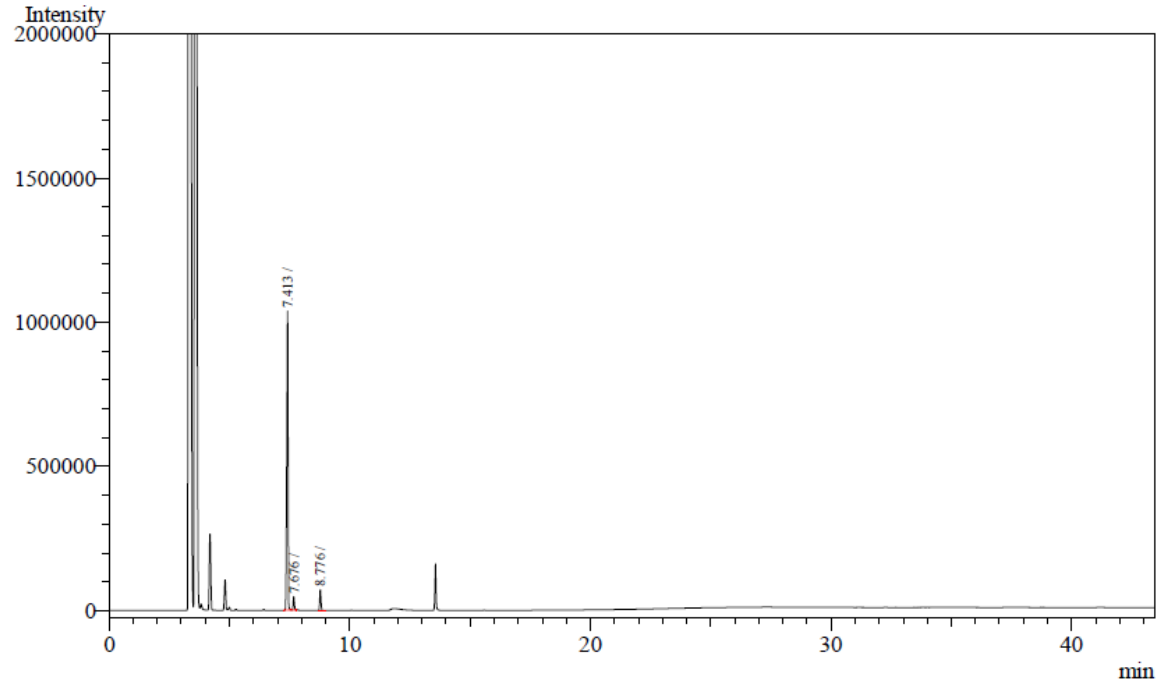
Chemical Formula: $C_{12}H_{15}F_3$
Exact Mass: 216.1126

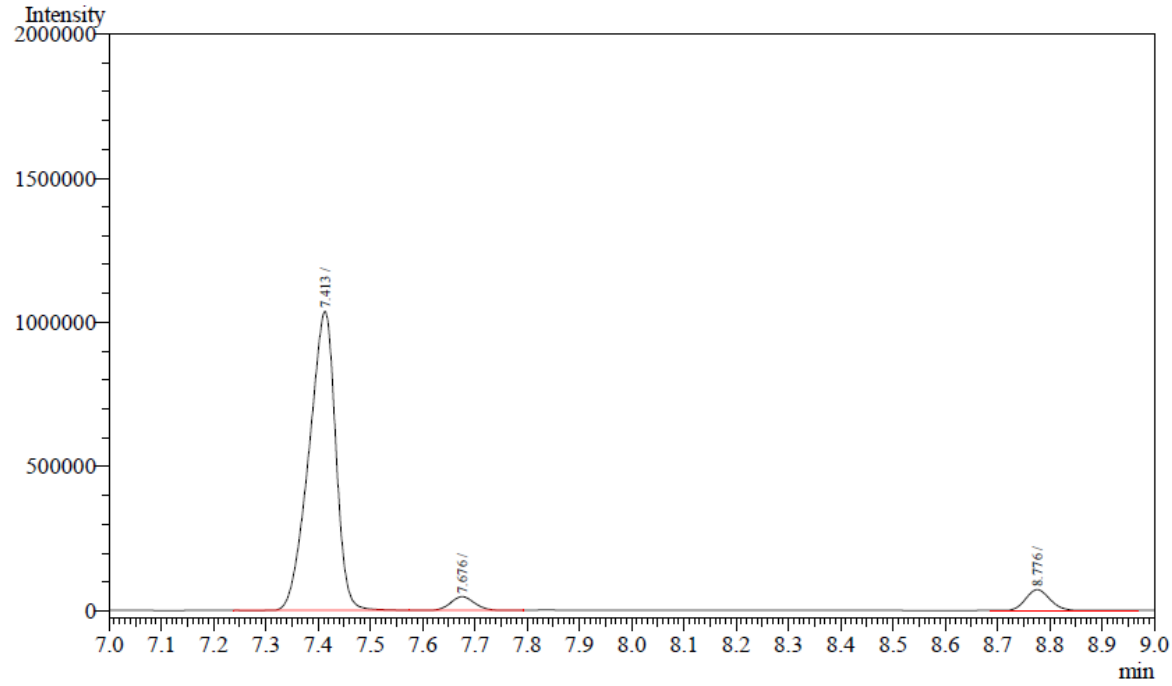
Obtained as the mixture of cross-coupling products according to the **general procedure F**.

From nonaflate: 133 mg colourless oil, 62% yield, 91:9.

From triflate: 183 mg colourless oil, 85% yield, 92:8.

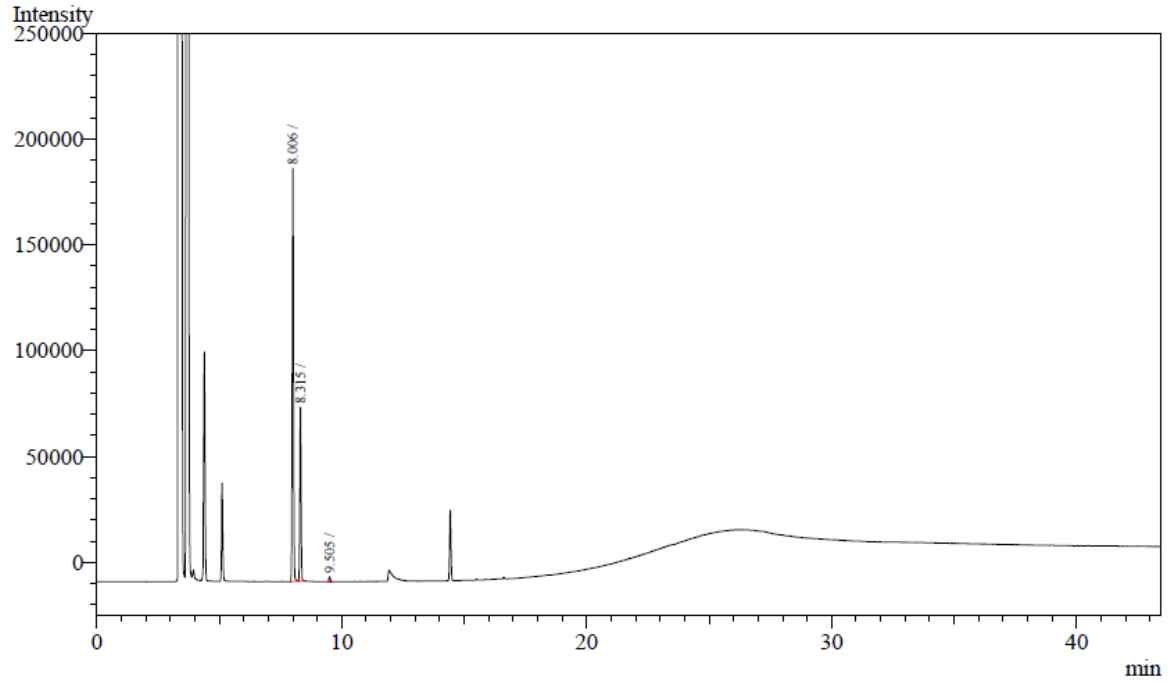
GC trace of the crude mixture using nonaflate as the substrate and L^{13} as the ligand

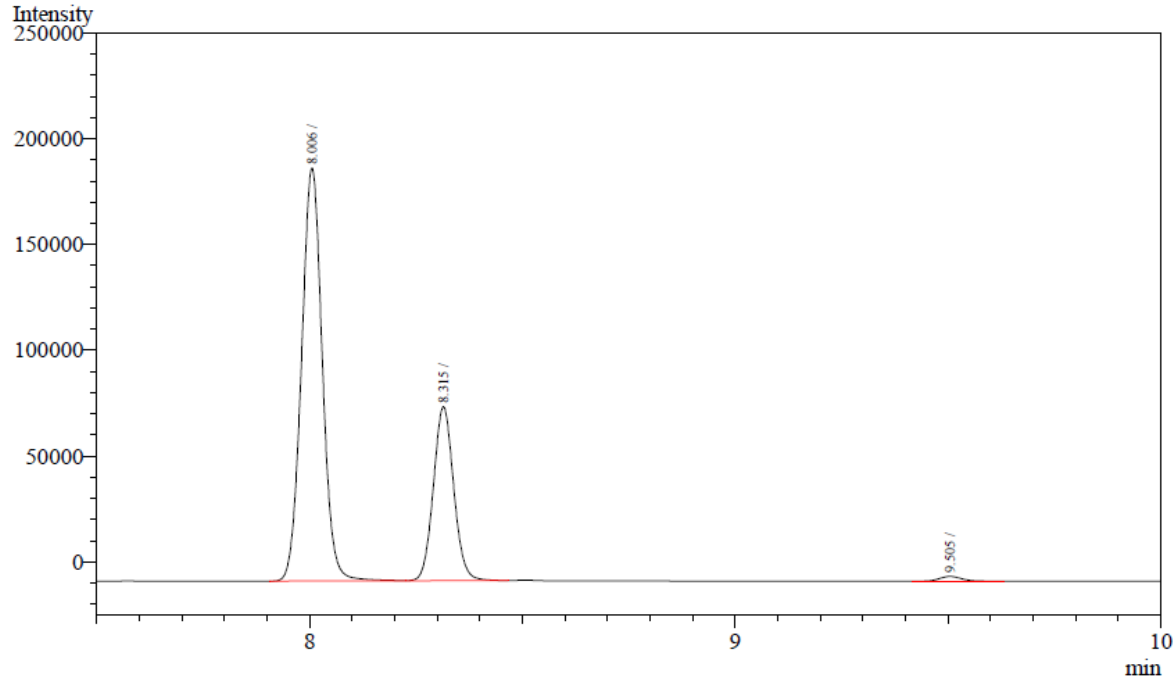




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	7.413	3686565	1034067	90.633	90.6326
2	7.676	144754	46637	3.559	3.5587
3	8.776	236274	72388	5.809	5.8087
Total		4067593	1153092	100.000	100.0000

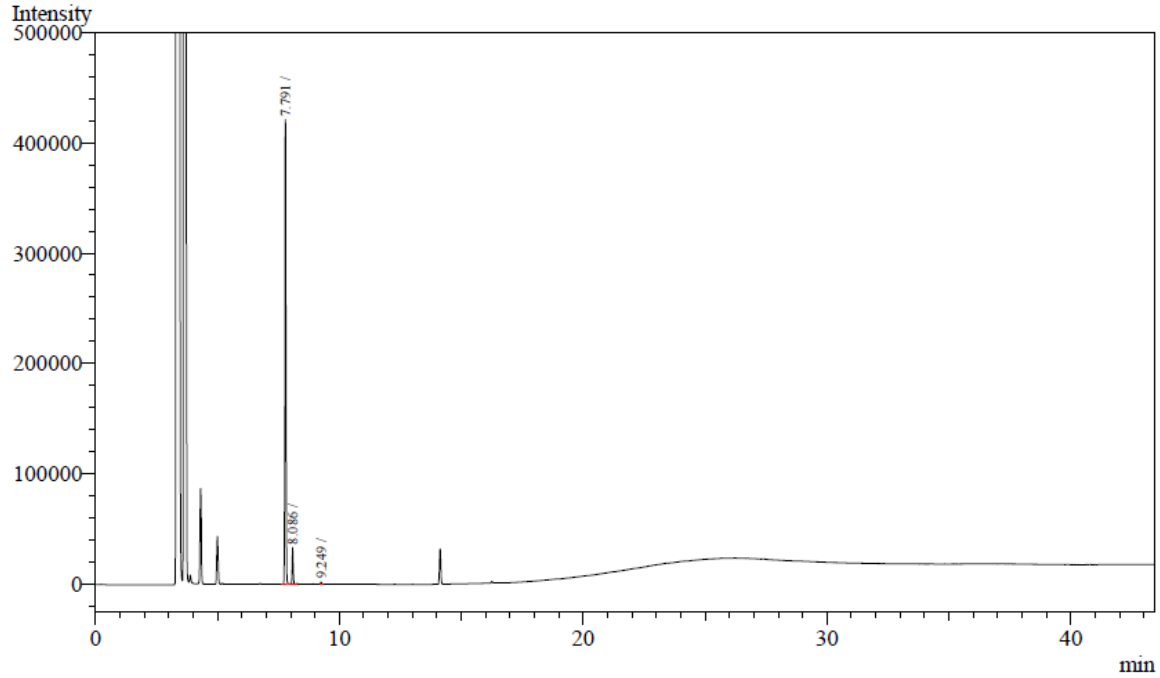
GC trace of the crude mixture using nonaflate as the substrate and CPhos as the ligand

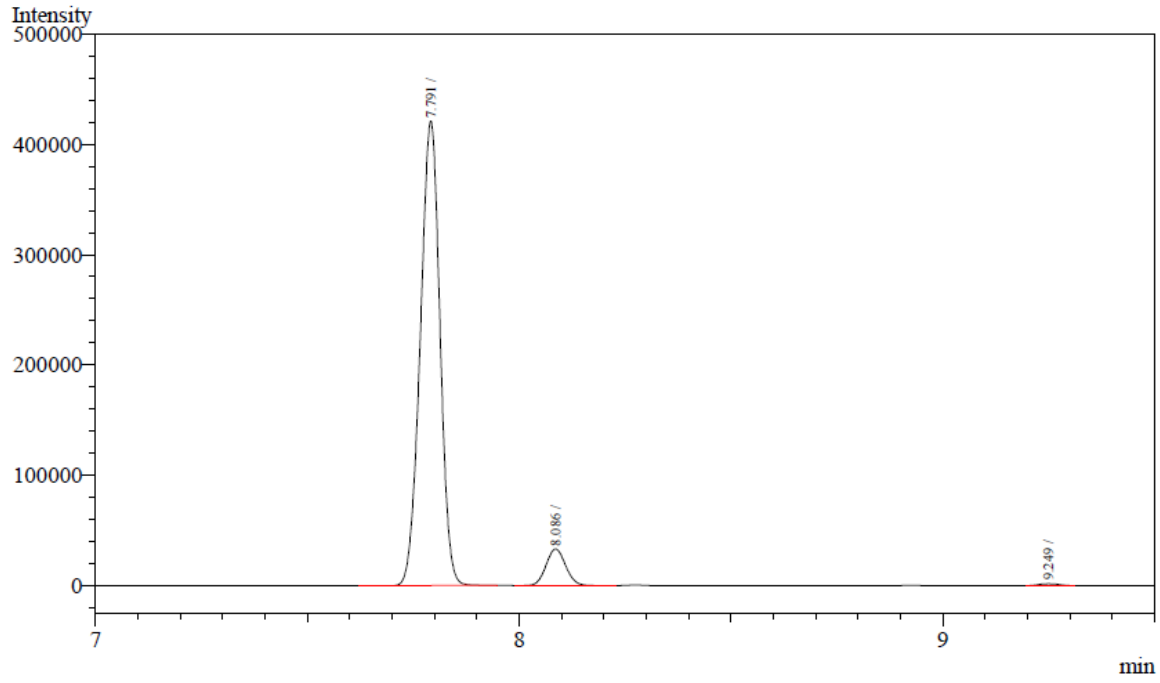




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	8.006	662038	194775	70.271	70.2709
2	8.315	272605	82032	28.935	28.9352
3	9.505	7480	2187	0.794	0.7940
Total		942123	278994	100.000	100.0000

GC trace of the crude mixture using triflate as the substrate and L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	7.791	1356356	420309	92.349	92.3494
2	8.086	106569	33119	7.256	7.2559
3	9.249	5798	1865	0.395	0.3948
Total		1468723	455293	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.48 – 7.30 (m, 4H), 2.46 – 2.34 (m, 1H), 1.79 – 1.67 (m, 2H), 1.62 – 1.51 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 6H).

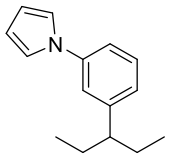
^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9, 131.4 (d, *J* = 1.4 Hz), 130.6 (q, *J* = 31.6 Hz), 128.7, 124.6 (d, *J* = 271.6 Hz), 124.6 (q, *J* = 3.8 Hz), 122.9 (d, *J* = 3.8 Hz), 49.8, 29.3, 12.2.

^{19}F NMR (376 MHz, $CDCl_3$) δ -62.5.

IR (neat): ν (cm^{-1}) 2923, 2855, 2366, 2143, 1462, 1378, 1327, 1168, 1131, 1074, 698.

GC-MS (EI) m/z for $C_{12}H_{15}F_3$ ($[M]^{+\bullet}$): 216.

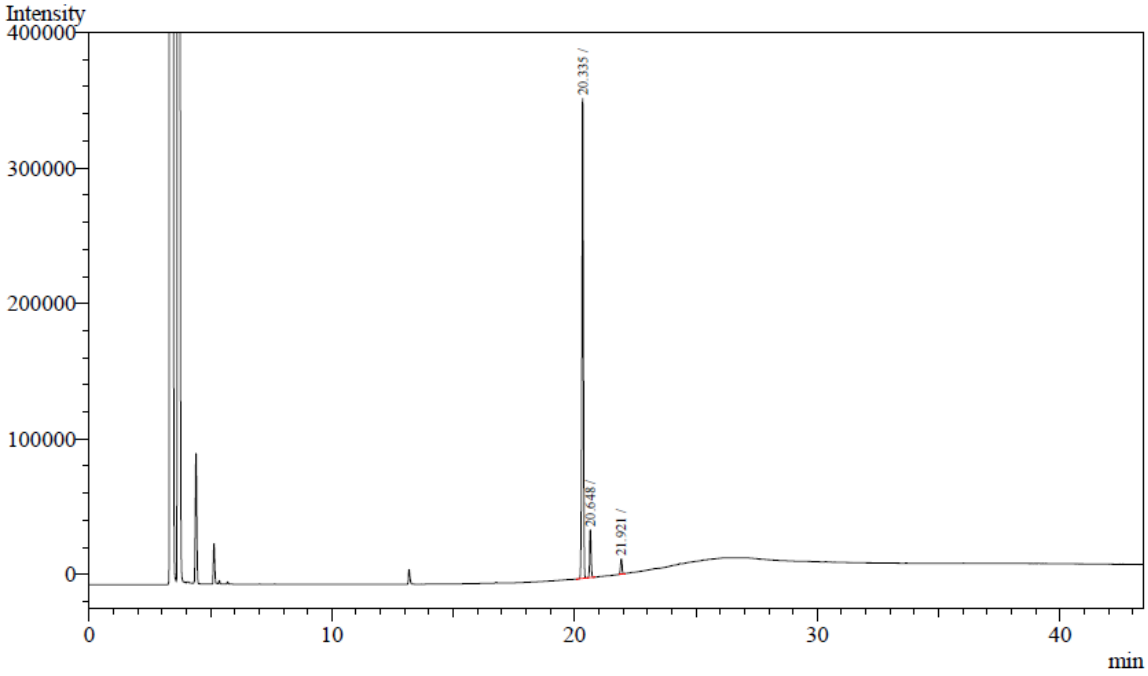
1-(3-(pentan-3-yl)phenyl)-1*H*-pyrrole 3-10j

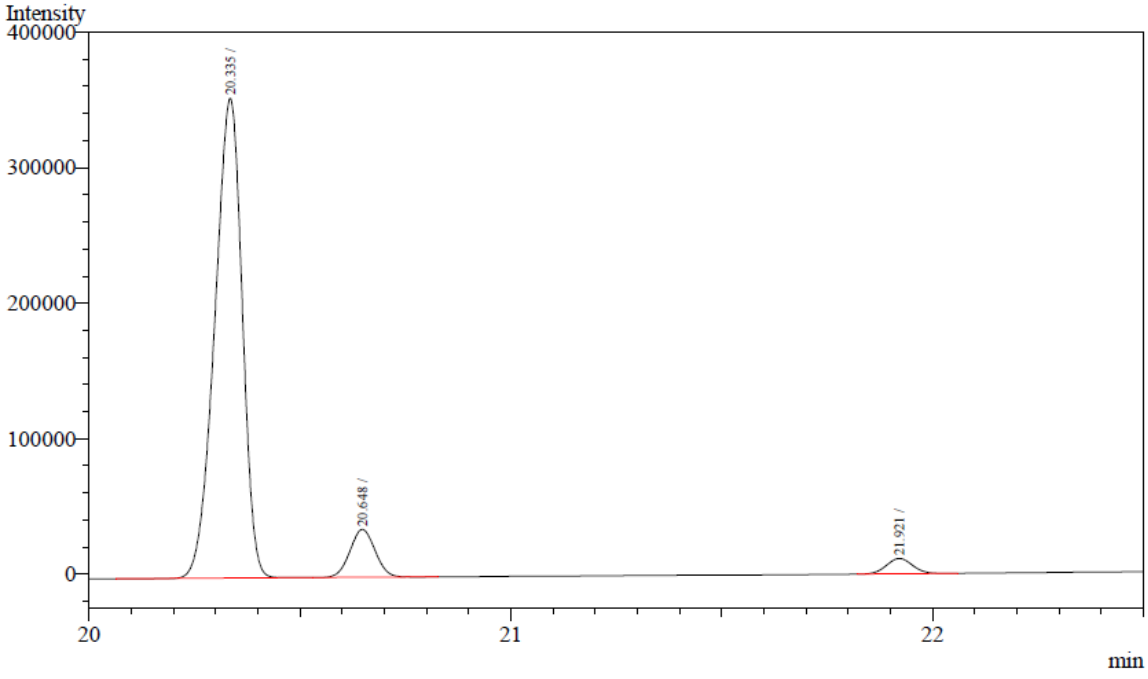


Chemical Formula: $C_{15}H_{19}N$
Exact Mass: 213.1517

Obtained as the mixture of cross-coupling products (138 mg colourless oil, 65% yield, 89:11) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.335	1598327	353153	89.142	89.1418
2	20.648	146389	35258	8.164	8.1644
3	21.921	48301	11235	2.694	2.6938
Total		1793017	399646	100.000	100.0000

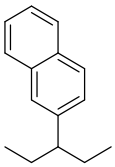
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.34 (t, *J* = 7.8 Hz, 1H), 7.22 (ddd, *J* = 8.0, 2.3, 1.1 Hz, 1H), 7.18 (t, *J* = 1.9 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.04 (dt, *J* = 7.6, 1.1 Hz, 1H), 6.36 (t, *J* = 2.2 Hz, 2H), 2.45 – 2.33 (m, 1H), 1.79 – 1.68 (m, 2H), 1.63 – 1.53 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 147.8, 140.9, 129.4, 125.4, 120.2, 119.5, 118.3, 110.3, 49.9, 29.4, 12.3.

IR (neat): ν (cm^{-1}) 2960, 2873, 1591, 1498, 1334, 1070, 1027, 949, 874, 789, 720.

HRMS (ESI): Calcd for $C_{15}H_{20}N$ $[M+H]^+$: 214.1590, found: 214.1590.

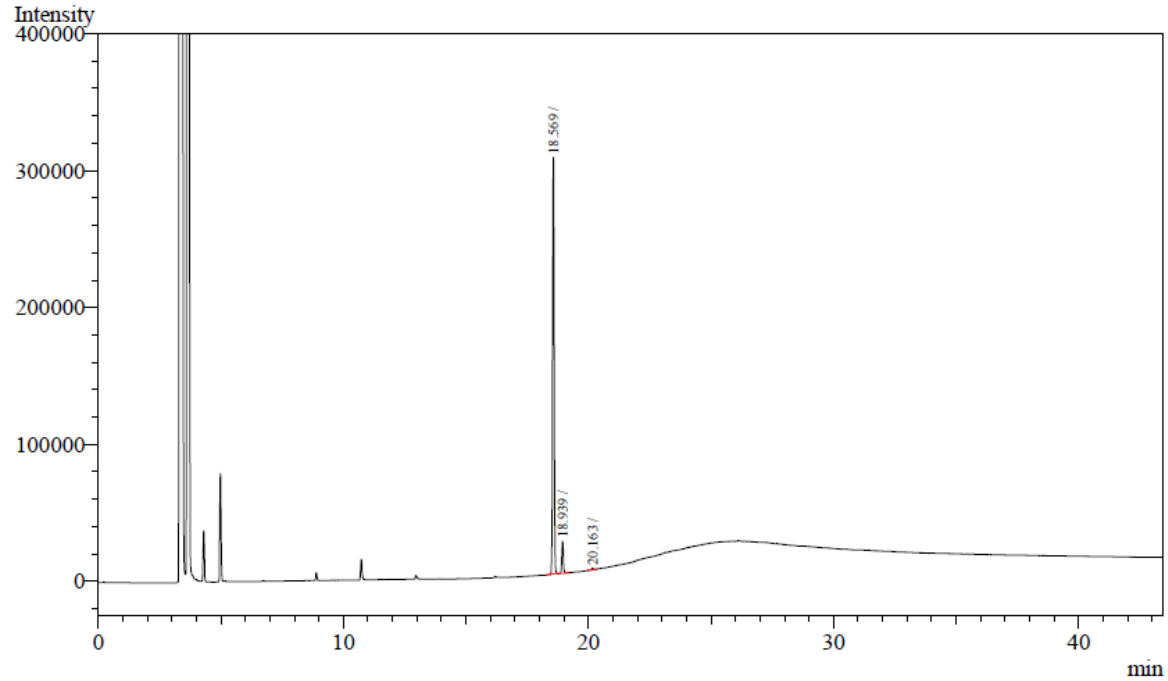
2-(pentan-3-yl)naphthalene 3-10k

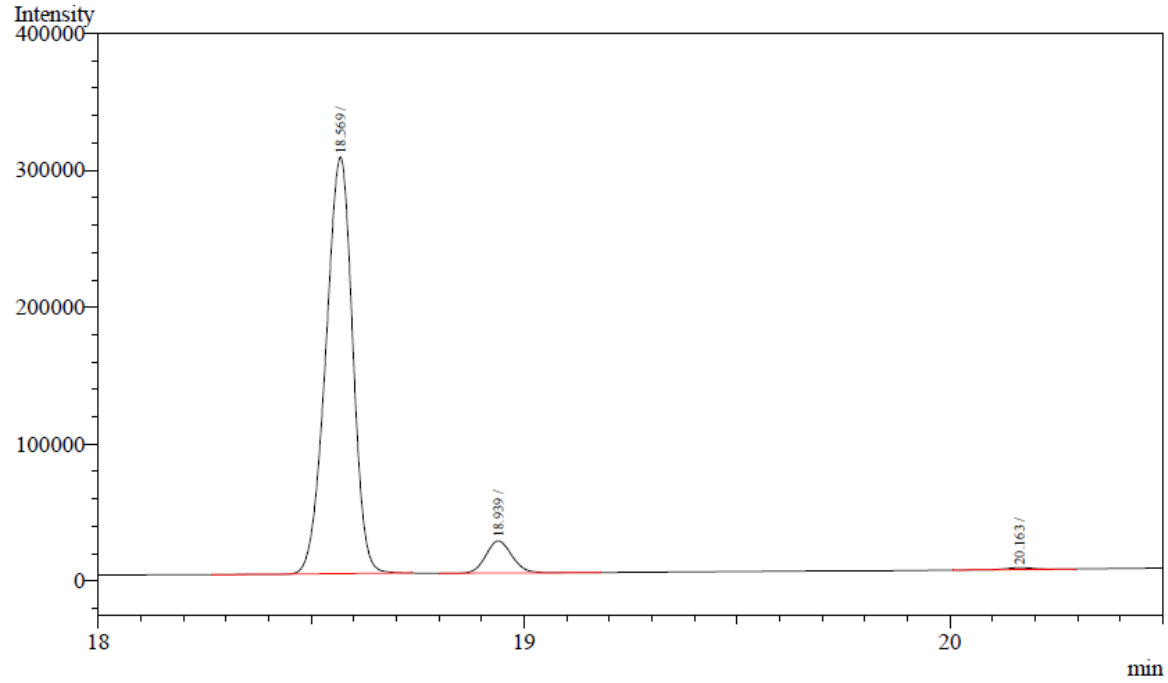


Chemical Formula: $C_{15}H_{18}$
Exact Mass: 198.1409

Obtained as the mixture of cross-coupling products (126 mg colourless oil, 64% yield, 93:7) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





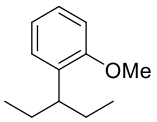
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	18.569	1330591	303321	92.720	92.7204
2	18.939	99044	23354	6.902	6.9017
3	20.163	5422	1204	0.378	0.3779
Total		1435057	327879	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.84 – 7.74 (m, 3H), 7.60 – 7.55 (m, 1H), 7.49 – 7.40 (m, 2H), 7.35 – 7.29 (m, 1H), 2.58 – 2.45 (m, 1H), 1.85 – 1.74 (m, 2H), 1.73 – 1.61 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 143.4, 133.7, 132.4, 127.9, 127.7, 127.6, 126.6, 126.2, 125.8, 125.1, 50.0, 29.4, 12.4.

The NMR data for this compound was consistent with literature data.[152]

1-methoxy-2-(pentan-3-yl)benzene 3-10l



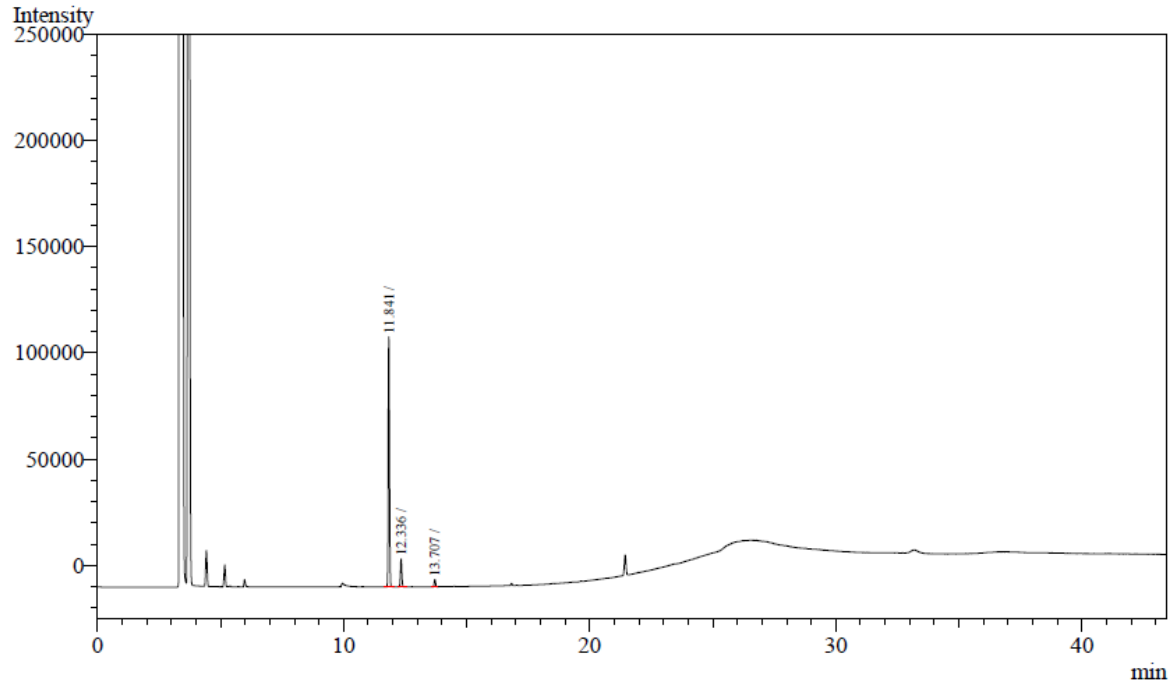
Chemical Formula: $C_{12}H_{18}O$
Exact Mass: 178.1358

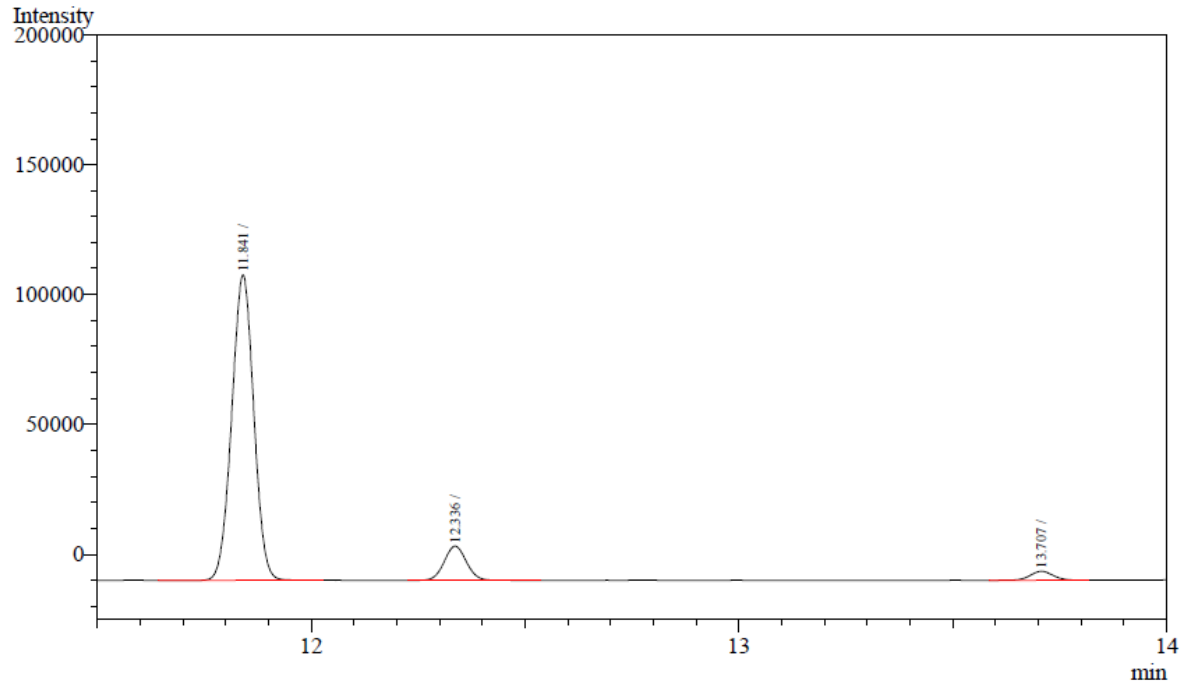
Obtained as the mixture of cross-coupling products according to the **general procedure F**.

From nonaflate: 156 mg colourless oil, 88% yield, 87:13.

From triflate (using 2.0 e.q. 3-bromopentane/Mg/LiCl/$ZnCl_2$): 140 mg colourless oil, 79% yield, 90:10

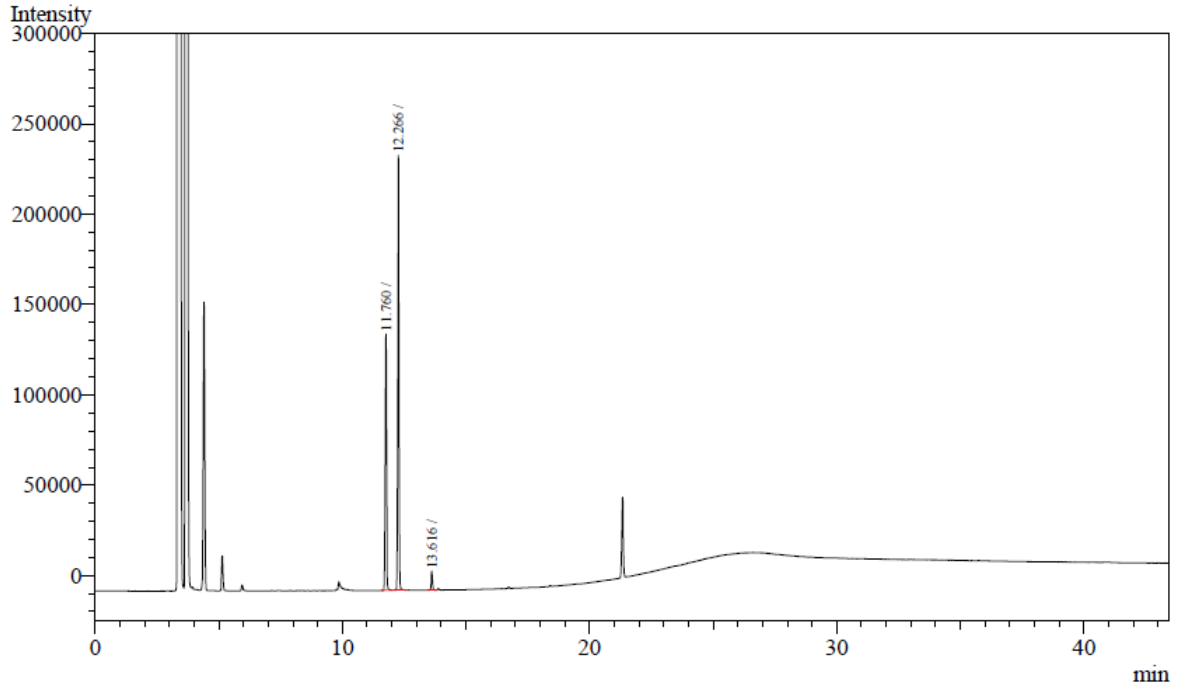
GC trace of the crude mixture using nonaflate as the substrate and L^{13} as the ligand

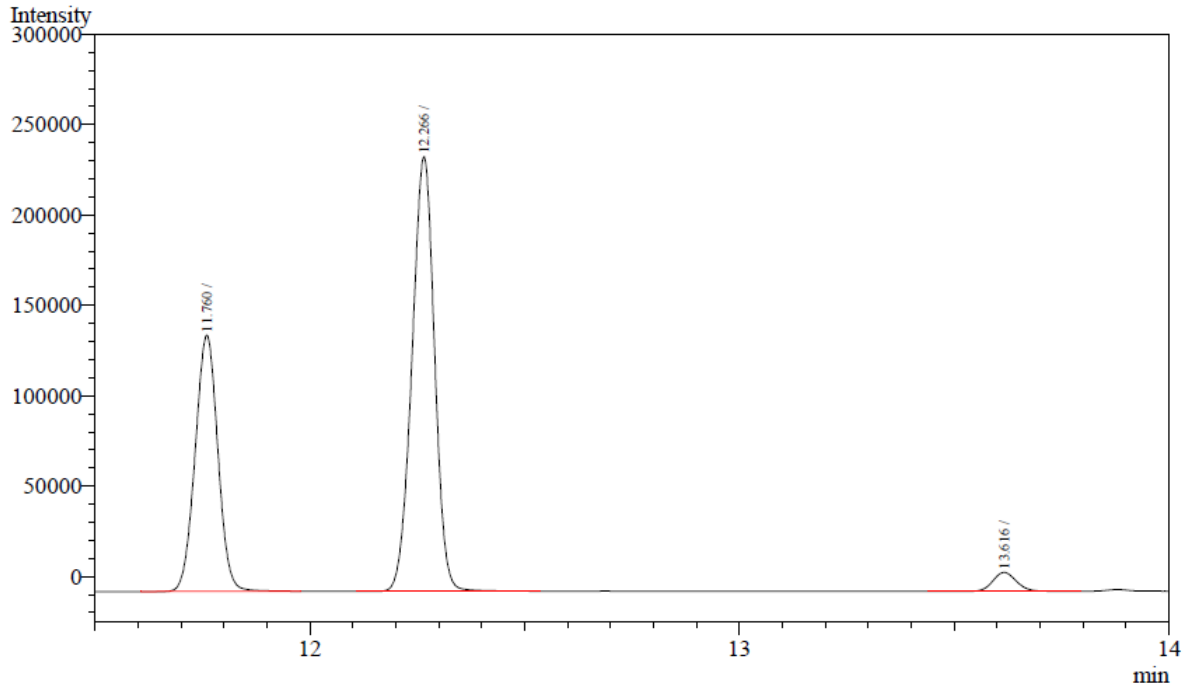




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	11.841	420932	117169	87.543	87.5430
2	12.336	47197	13127	9.816	9.8158
3	13.707	12699	3414	2.641	2.6412
Total		480828	133710	100.000	100.0000

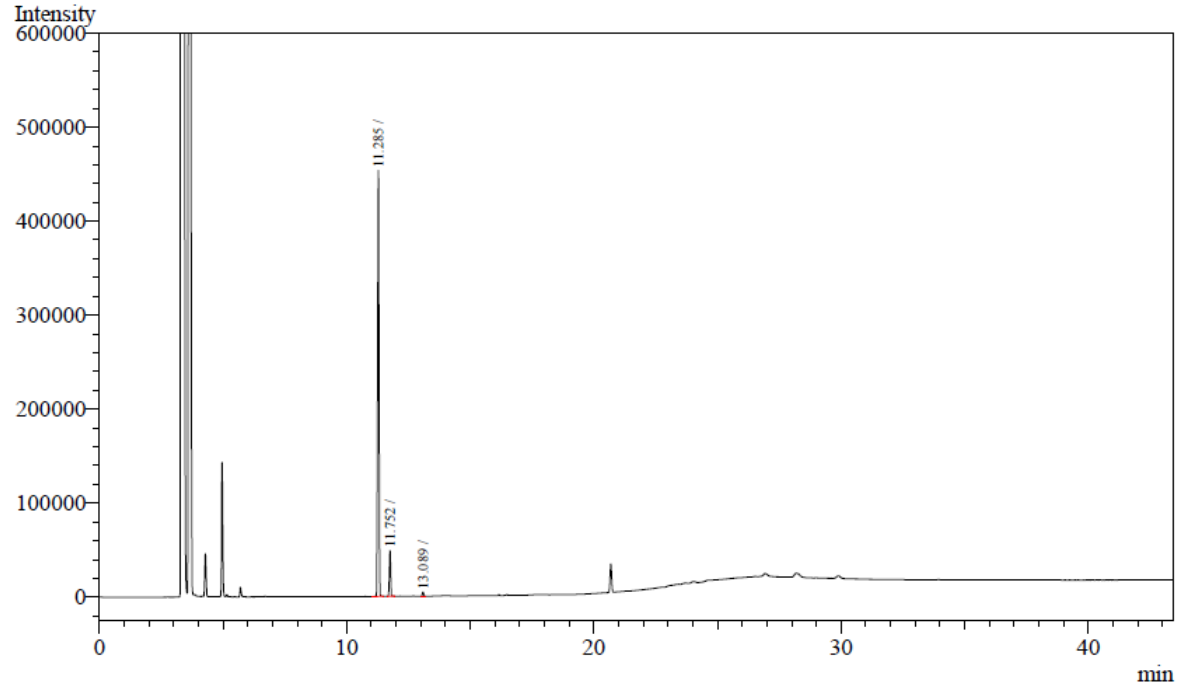
GC trace of the crude mixture using nonaflate as the substrate and CPhos as the ligand

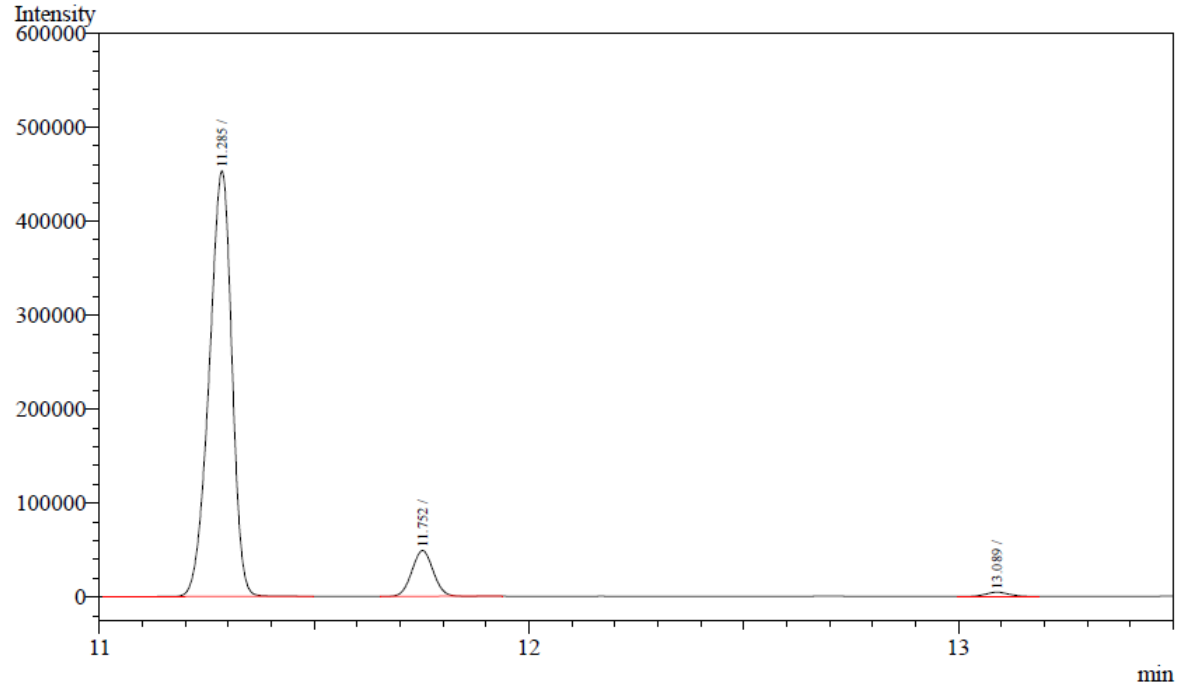




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	11.760	520223	141067	36.226	36.2259
2	12.266	877093	239770	61.077	61.0768
3	13.616	38735	10393	2.697	2.6973
Total		1436051	391230	100.000	100.0000

GC trace of the crude mixture using triflate as the substrate and L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	11.285	1655908	450736	90.025	90.0247
2	11.752	167579	48441	9.111	9.1106
3	13.089	15905	4423	0.865	0.8647
Total		1839392	503600	100.000	100.0000

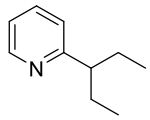
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.19 – 7.09 (m, 2H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 8.1 Hz, 1H), 3.81 (s, 3H), 3.00 – 2.88 (m, 1H), 1.72 – 1.62 (m, 2H), 1.61 – 1.53 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 134.3, 127.6, 126.5, 120.6, 110.7, 55.6, 41.0, 28.1, 12.2.

IR (neat): ν (cm^{-1}) 2960, 2873, 1599, 1460, 1377, 1237, 1173, 1099, 1032, 748.

GC-MS (EI) m/z for $C_{12}H_{18}O$ ($[M]^{+\bullet}$): 178.

2-(pentan-3-yl)pyridine 3-10m

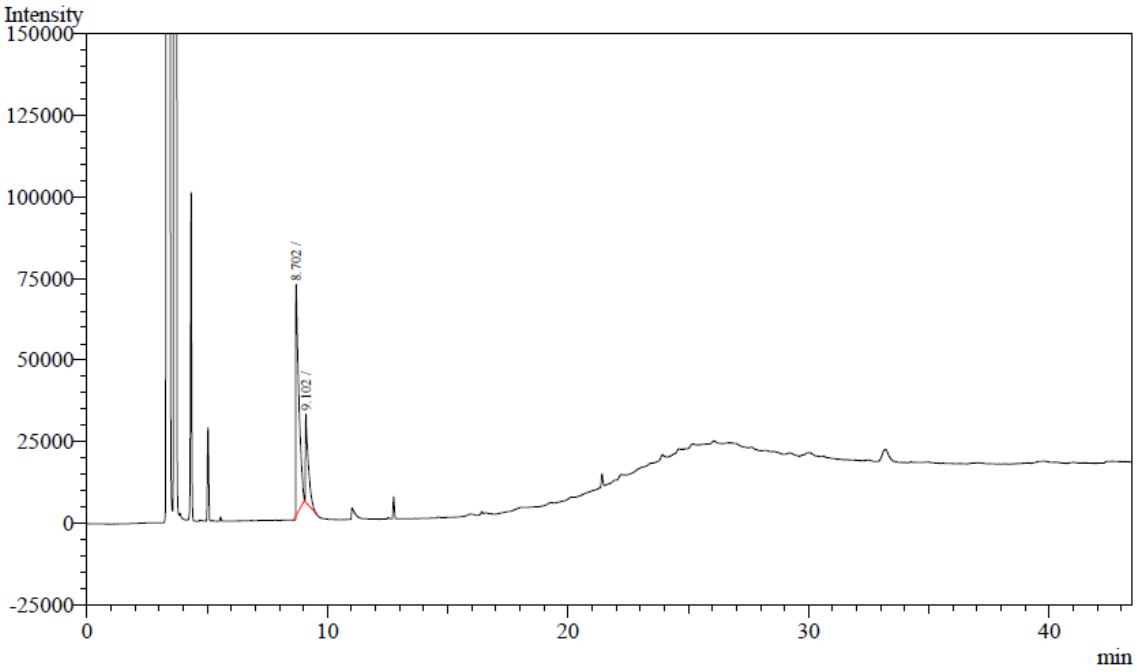


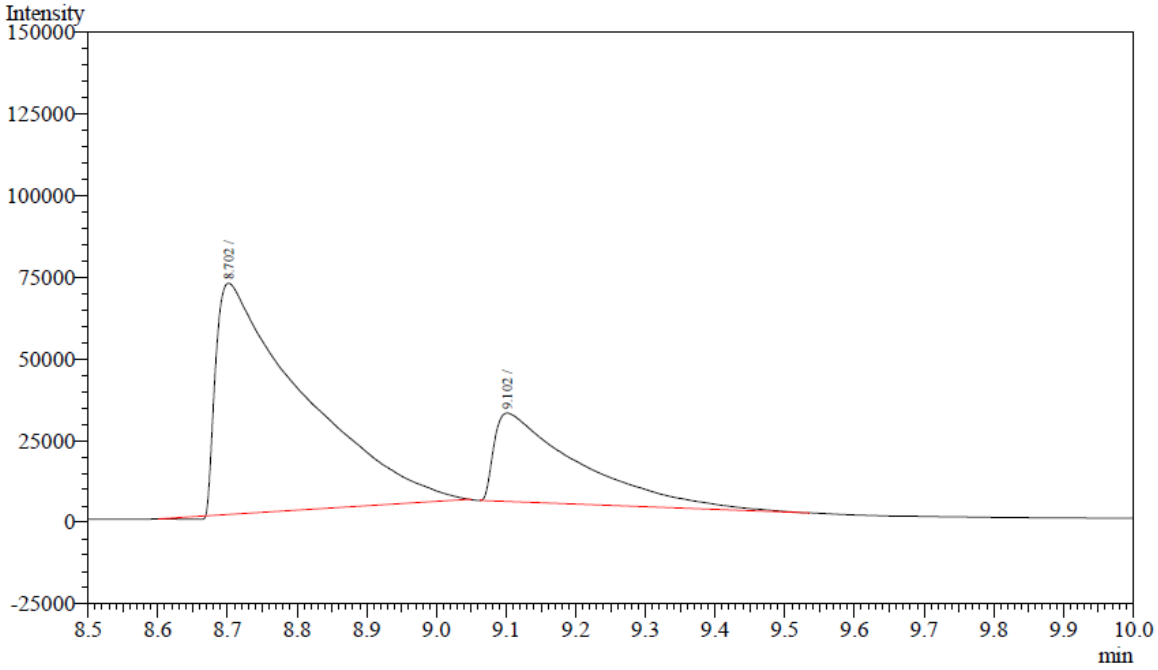
Chemical Formula: $C_{10}H_{15}N$
Exact Mass: 149.1204

Obtained as the mixture of cross-coupling products (90.8 mg colourless oil, 61% yield, 72:28) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand

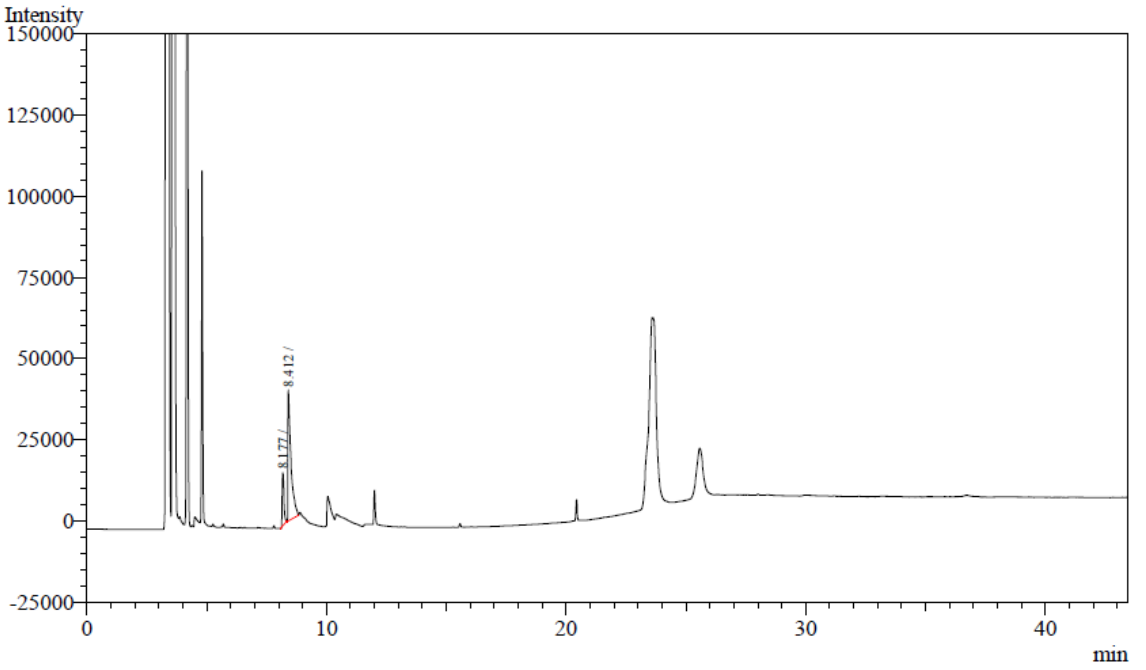
(The ratio could also be measured by **^{1}H-NMR**, see the spectrum below)

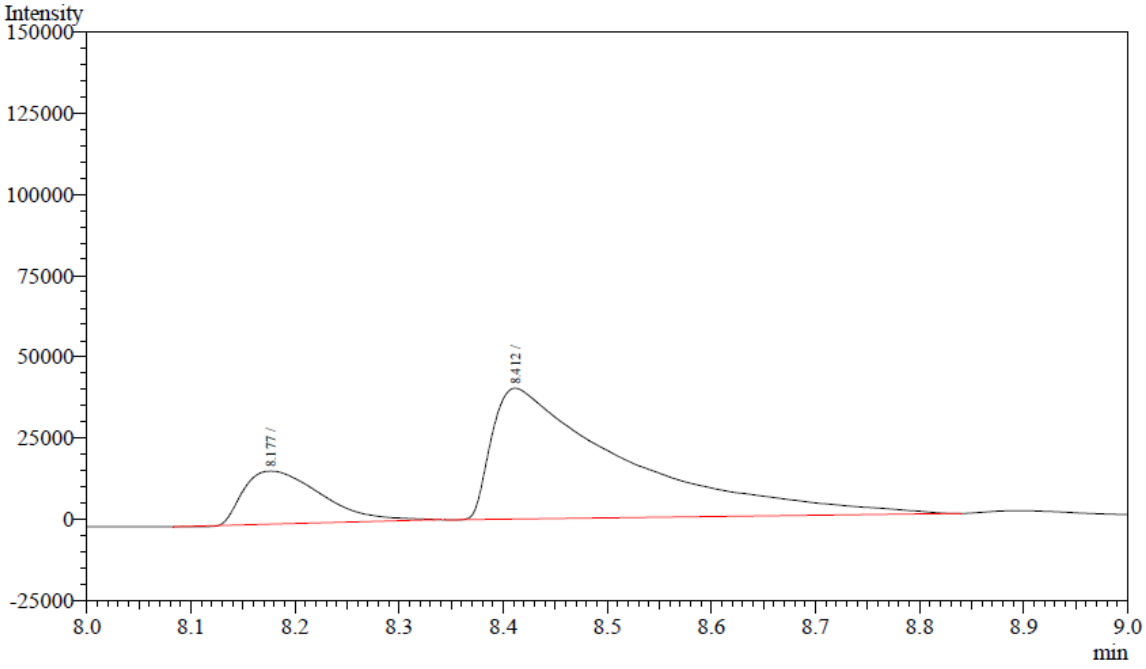




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	8.702	617436	70757	73.105	73.1053
2	9.102	227149	27003	26.895	26.8947
Total		844585	97760	100.000	100.0000

GC trace of the crude mixture with CPhos as the ligand



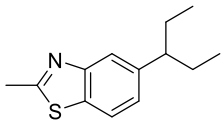


Peak#	Ret.Time	Area	Height	Conc.	Area%
1	8.177	84239	16283	19.133	19.1325
2	8.412	356052	40169	80.867	80.8675
Total		440291	56452	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.57 – 8.53 (m, 1H), 7.60 – 7.53 (m, 1H), 7.09 – 7.04 (m, 2H), 2.59 – 2.46 (m, 1H), 1.75 – 1.65 (m, 4H), 0.77 (t, *J* = 7.4 Hz, 6H).

The NMR data for this compound was consistent with literature data.[153]

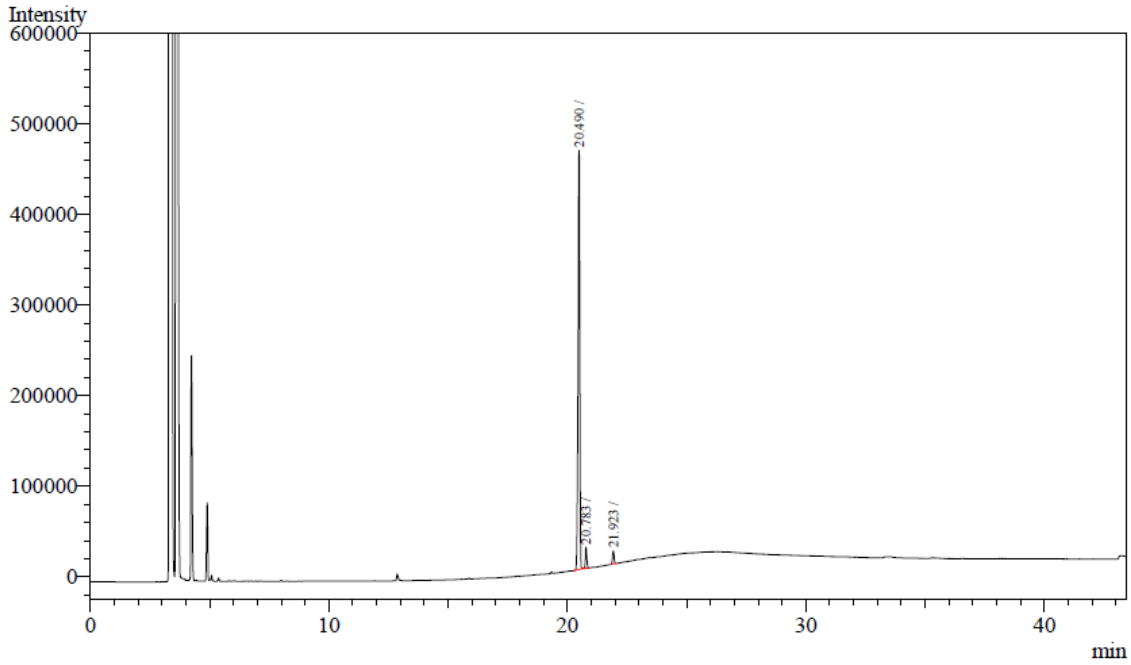
2-methyl-5-(pentan-3-yl)benzo[d]thiazole 3-10n

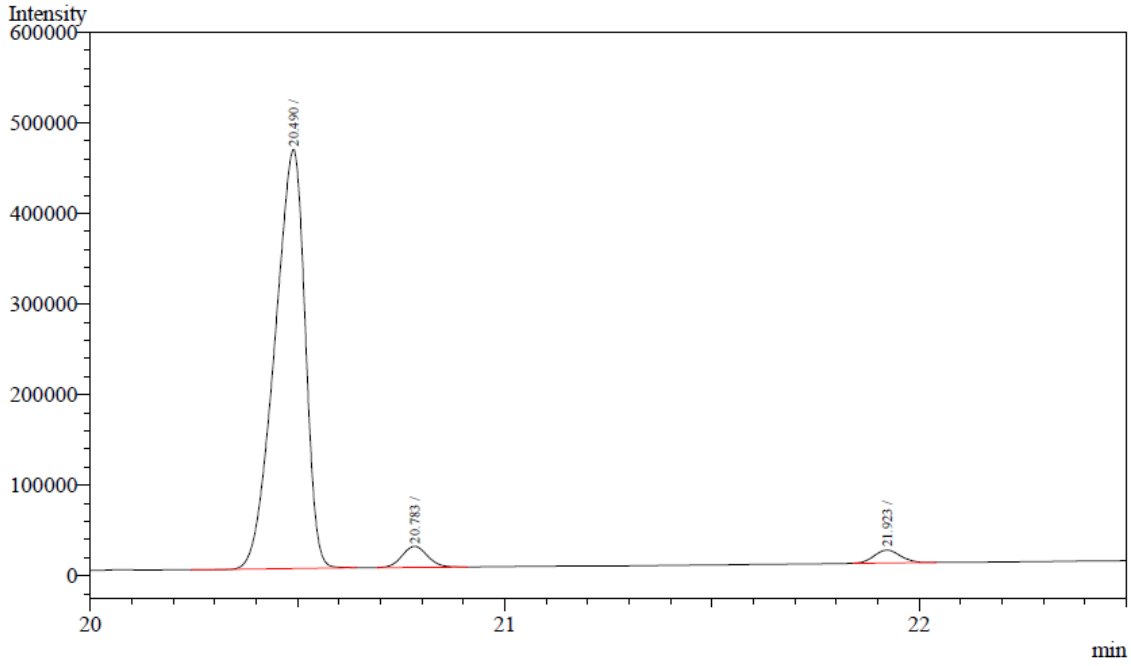


Chemical Formula: $C_{13}H_{17}NS$
Exact Mass: 219.1082

Obtained as the mixture of cross-coupling products (148 mg colourless oil, 68% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.490	2352022	462092	93.590	93.5896
2	20.783	98413	23223	3.916	3.9160
3	21.923	62688	14193	2.494	2.4944
Total		2513123	499508	100.000	100.0000

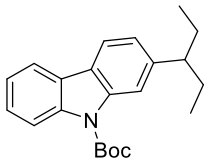
^{1}H NMR (400 MHz, Chloroform-*d*) δ (ppm) 7.79 – 7.66 (m, 2H), 7.15 (dd, *J* = 8.2, 1.7 Hz, 1H), 2.82 (s, 3H), 2.51 – 2.40 (m, 1H), 1.81 – 1.69 (m, 2H), 1.66 – 1.55 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ (ppm) 167.0, 153.9, 144.3, 133.1, 125.2, 121.5, 121.0, 49.8, 29.6, 20.2, 12.3.

IR (neat): ν (cm^{-1}) 2958, 2924, 2872, 1527, 1457, 1375, 1308, 1248, 1172, 1074, 938, 880, 809, 643.

HRMS (ESI): Calcd for $C_{13}H_{18}NS$ $[M+H]^+$: 220.1154, found: 220.1154.

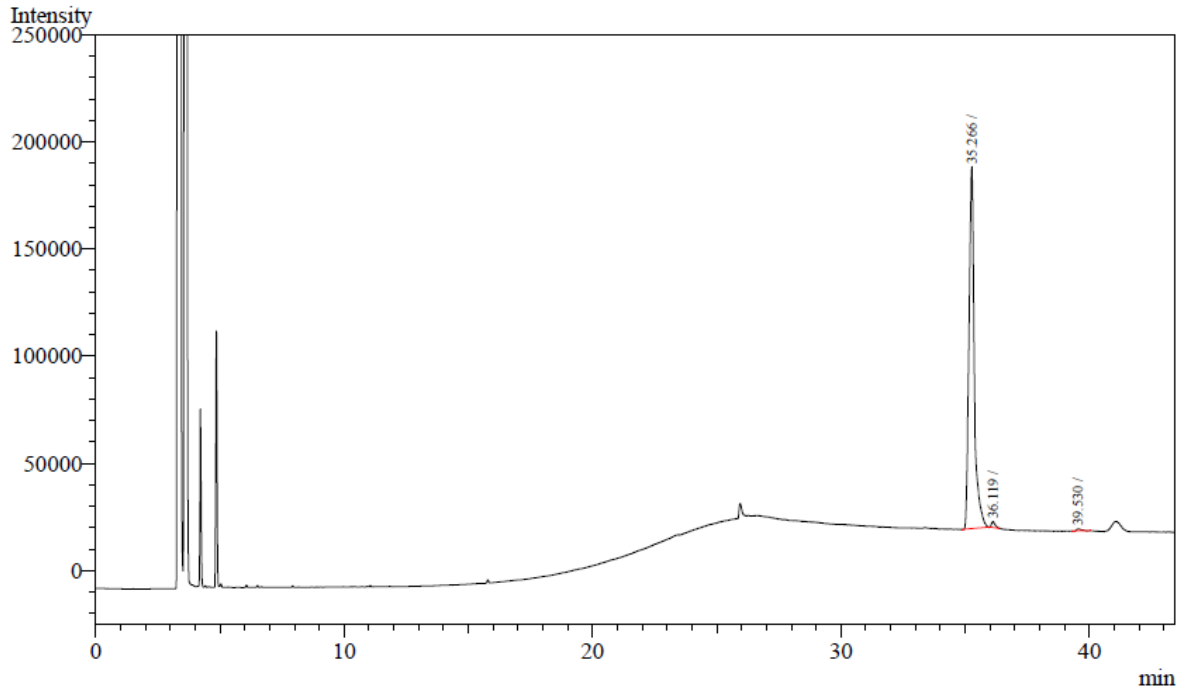
***tert*-butyl 2-(pentan-3-yl)-9H-carbazole-9-carboxylate 3-10o**

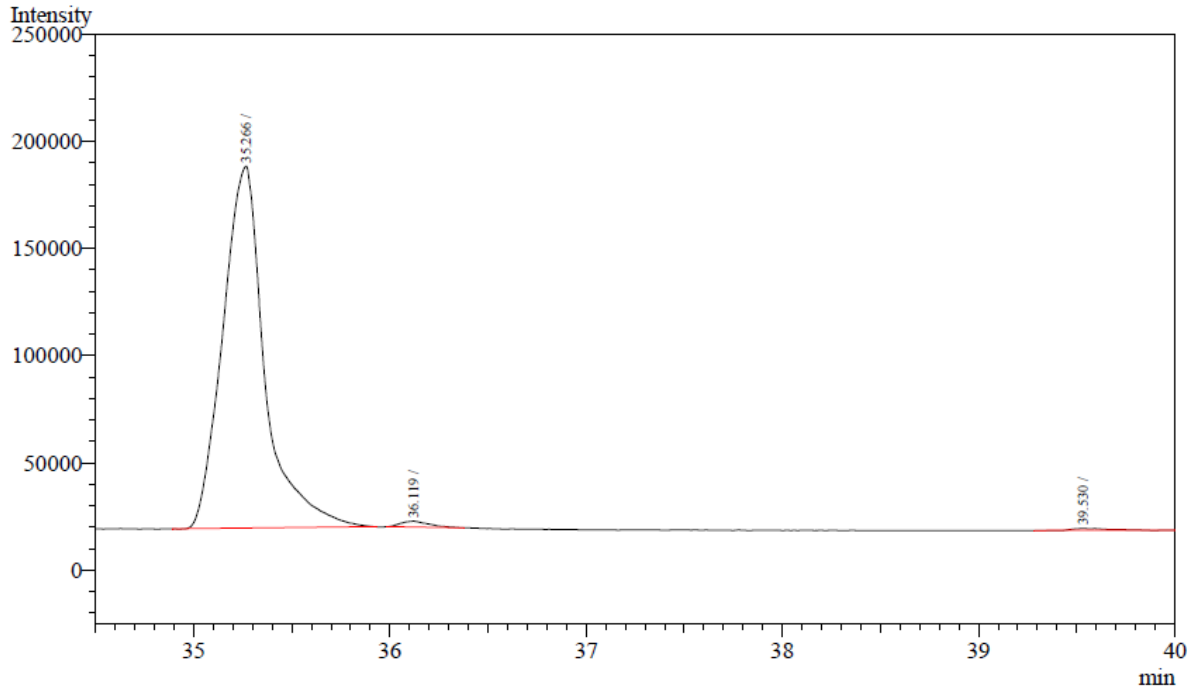


Chemical Formula: $C_{22}H_{27}NO_2$
Exact Mass: 337.2042

Obtained as the mixture of cross-coupling products (323 mg colourless oil, 96% yield, 99:1) according to the **general procedure F**.

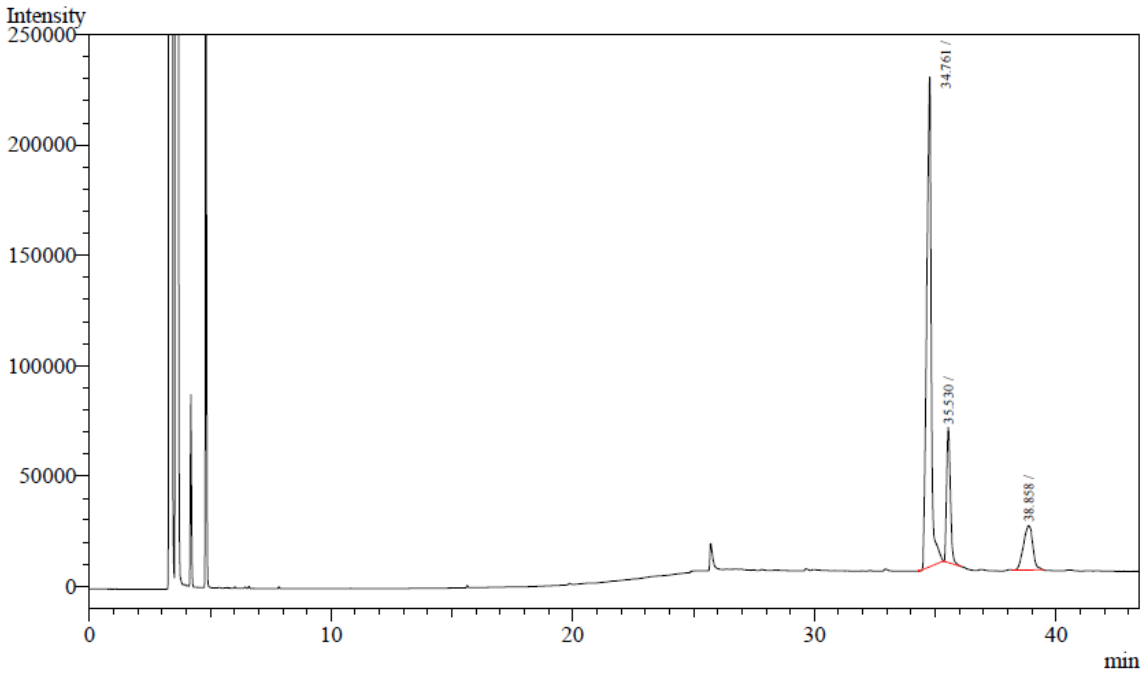
GC trace of the crude mixture using L^{13} as the ligand

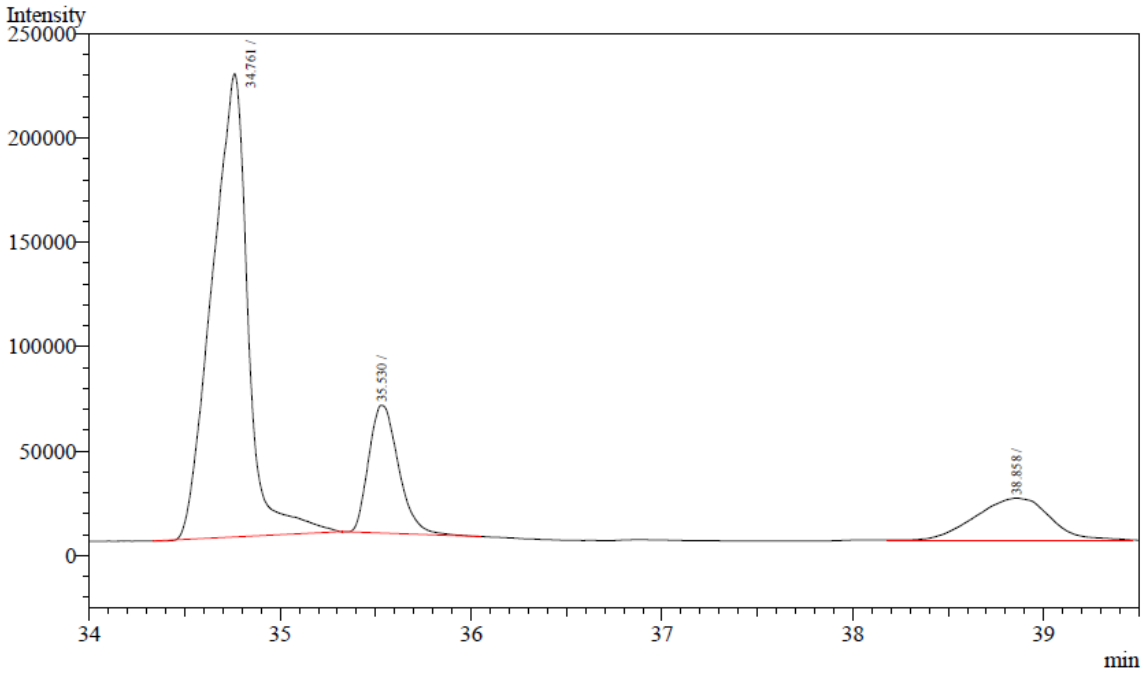




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	35.266	2518916	168808	98.467	98.4667
2	36.119	27709	2746	1.083	1.0832
3	39.530	11515	905	0.450	0.4501
Total		2558140	172459	100.000	100.0000

GC trace of the crude mixture using CPhos as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	34.761	2909272	221848	70.632	70.6320
2	35.530	668599	61271	16.232	16.2324
3	38.858	541045	20143	13.136	13.1356
Total		4118916	303262	100.000	100.0000

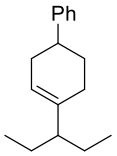
^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 – 8.24 (m, 1H), 8.17 – 8.09 (m, 1H), 7.98 – 7.91 (m, 1H), 7.91 – 7.84 (m, 1H), 7.46 – 7.38 (m, 1H), 7.36 – 7.29 (m, 1H), 7.20 – 7.11 (m, 1H), 2.56 – 2.45 (m, 1H), 1.87 – 1.70 (m, 11H), 1.70 – 1.61 (m, 2H), 0.82 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 151.4, 145.6, 139.1, 138.7, 126.6, 126.1, 124.0, 123.2, 123.0, 119.4, 119.2, 116.4, 115.7, 83.8, 50.6, 29.8, 28.6, 12.5.

IR (neat): ν (cm^{-1}) 2964, 2928, 1727, 1458, 1364, 1221, 1158, 767.

HRMS (ESI): Calcd for $C_{22}H_{27}NNaO_2$ $[M+Na]^+$: 360.1934, found: 360.1934.

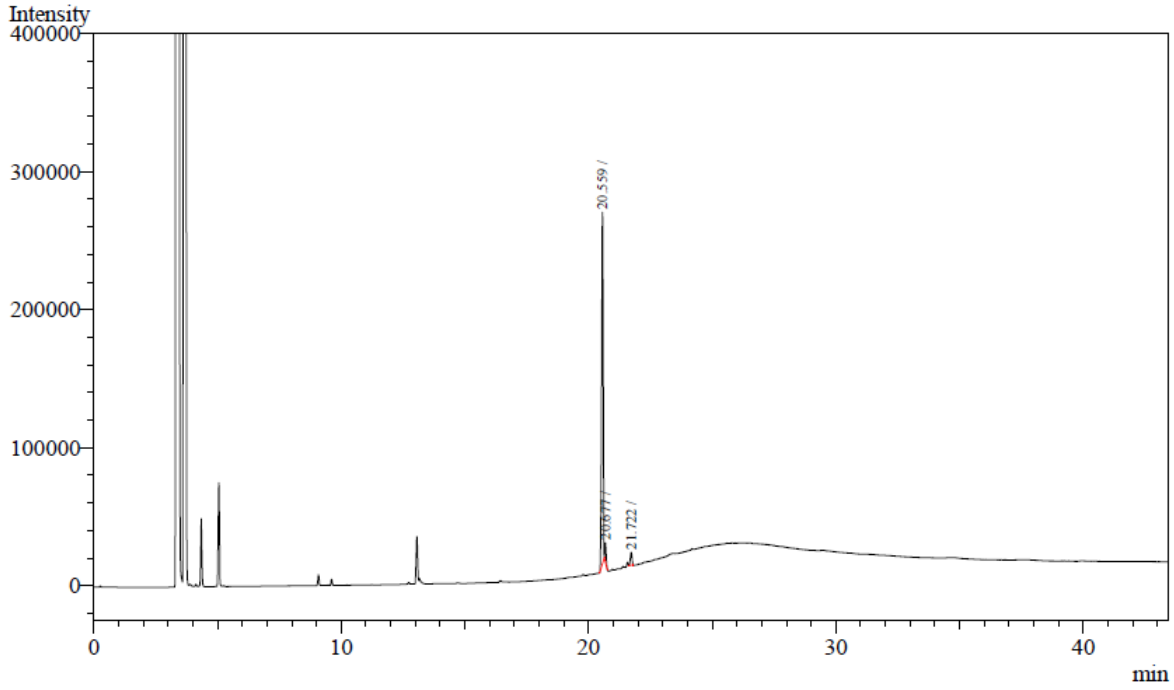
4-(pentan-3-yl)-1,2,3,6-tetrahydro-1,1'-biphenyl 3-10p

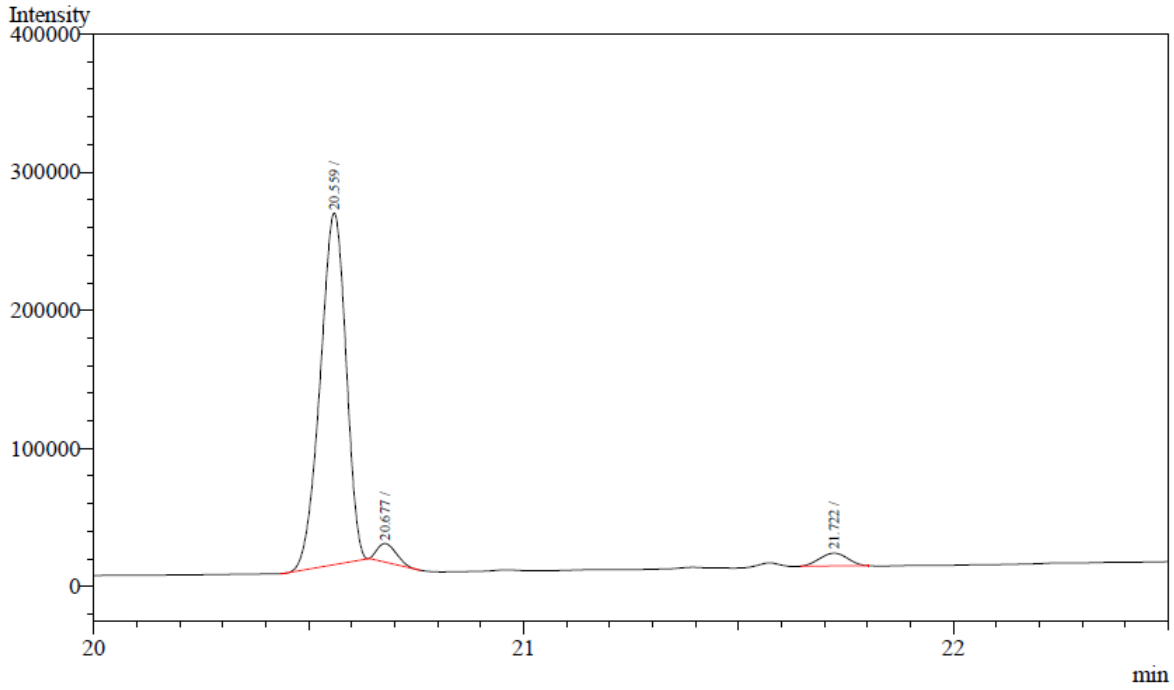


Chemical Formula: $C_{17}H_{24}$
Exact Mass: 228.1878

Obtained as the mixture of cross-coupling products (141 mg pale yellow oil, 62% yield, 93:7) according to the **general procedure F**.

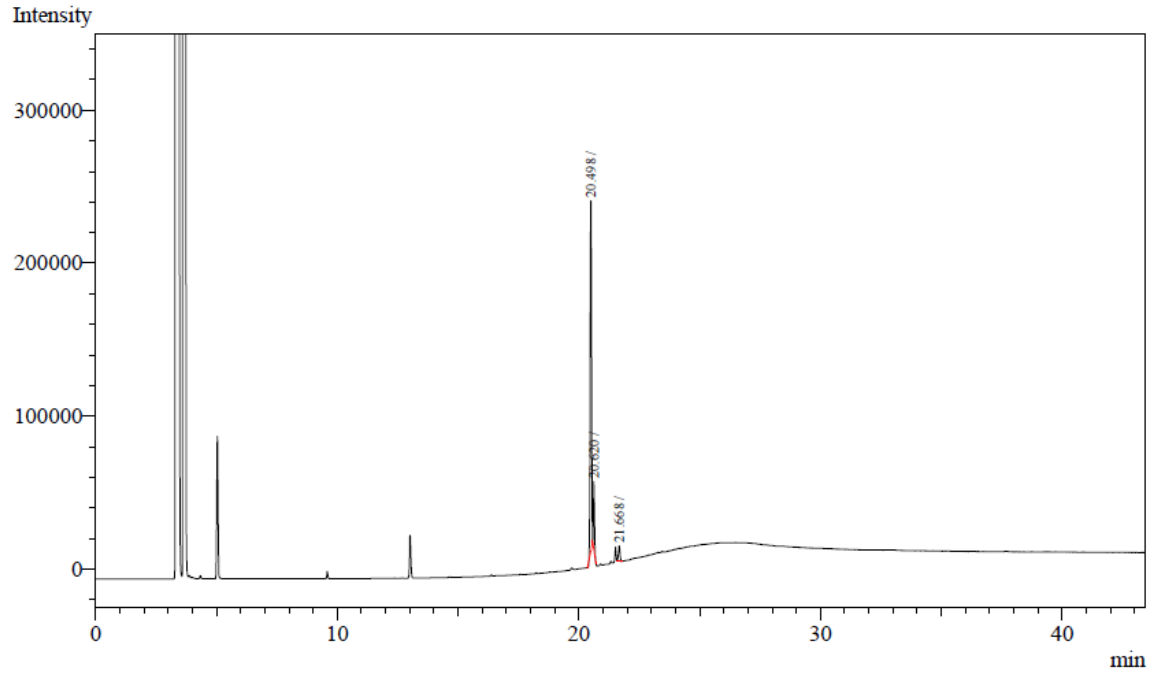
GC trace of the crude mixture using L^{13} as the ligand

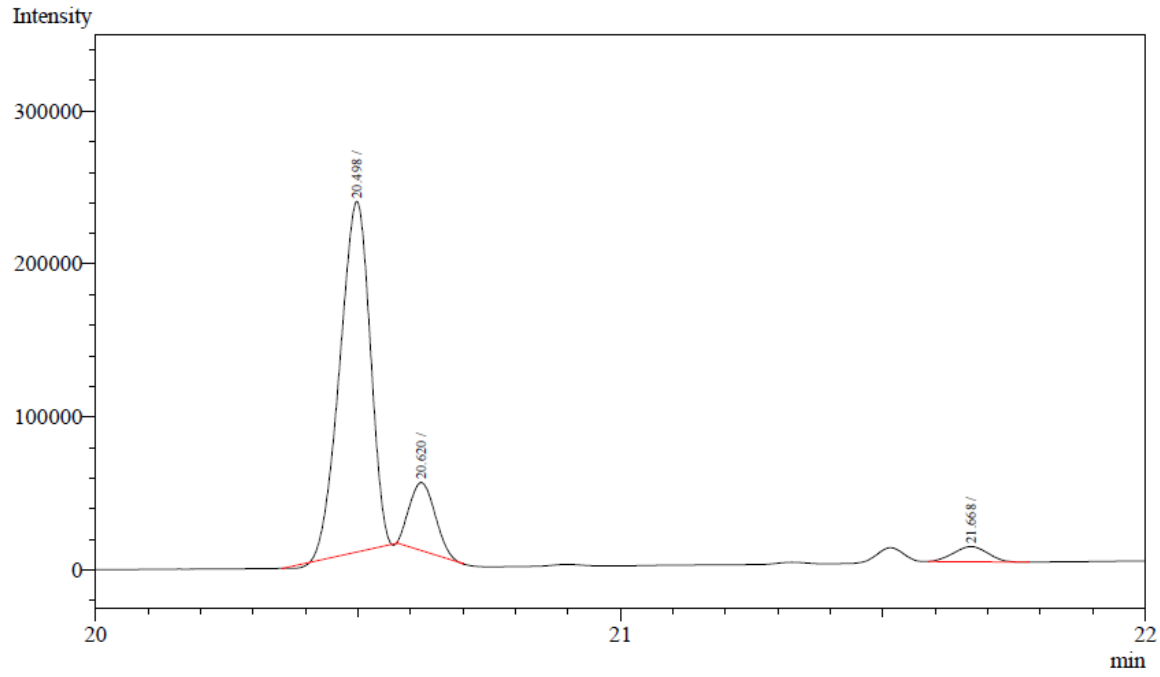




Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.559	1060926	254257	92.688	92.6884
2	20.677	41471	13344	3.623	3.6231
3	21.722	42219	9313	3.688	3.6885
Total		1144616	276914	100.000	100.0000

GC trace of the crude mixture using CPhos as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.498	918030	228842	82.325	82.3245
2	20.620	151891	44380	13.621	13.6208
3	21.668	45215	9940	4.055	4.0547
Total		1115136	283162	100.000	100.0000

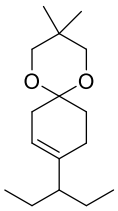
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.18 (m, 5H), 5.55 – 5.41 (m, 1H), 2.86 – 2.70 (m, 1H), 2.40 – 2.14 (m, 2H), 2.05 – 1.90 (m, 3H), 1.81 – 1.68 (m, 2H), 1.43 – 1.29 (m, 4H), 0.89 – 0.77 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 147.6, 139.3, 128.4, 127.1, 126.0, 122.1, 51.2, 40.7, 33.7, 30.3, 26.4, 26.2, 24.7, 12.4.

IR (neat): ν (cm^{-1}) 2960, 2927, 2874, 2363, 2126, 1494, 1454, 757, 698, 654.

GC-MS (EI) m/z for $C_{17}H_{24}$ ($[M]^{+\bullet}$): 228.

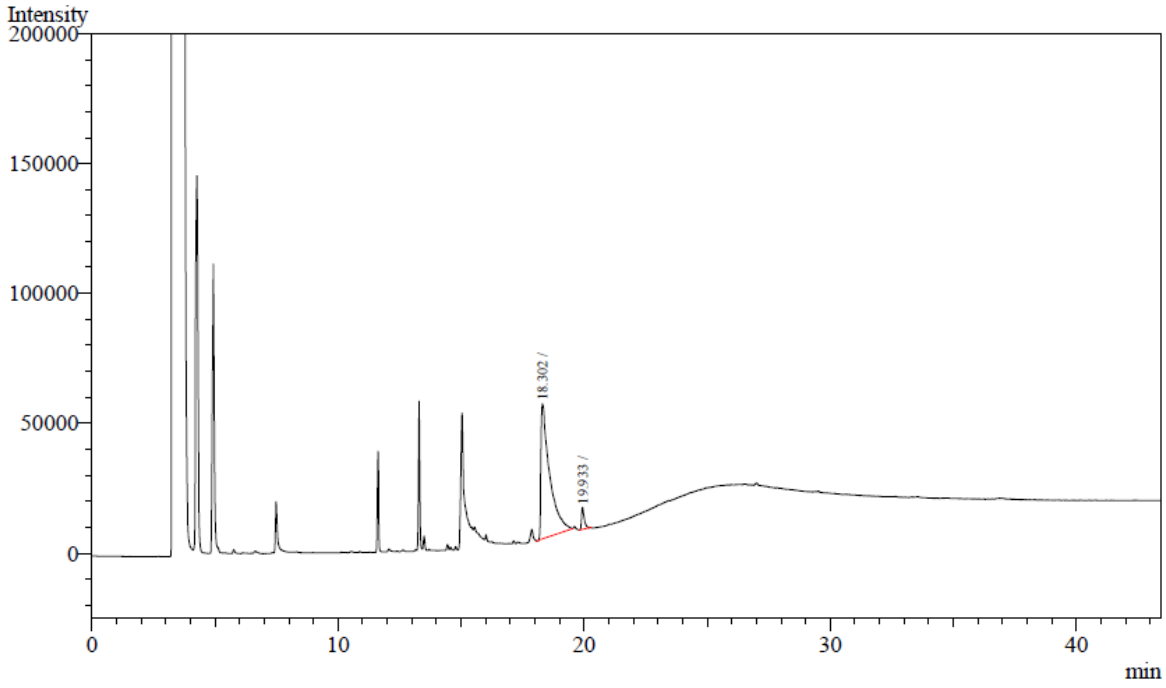
3,3-dimethyl-9-(pentan-3-yl)-1,5-dioxaspiro[5.5]undec-8-ene 3-10q

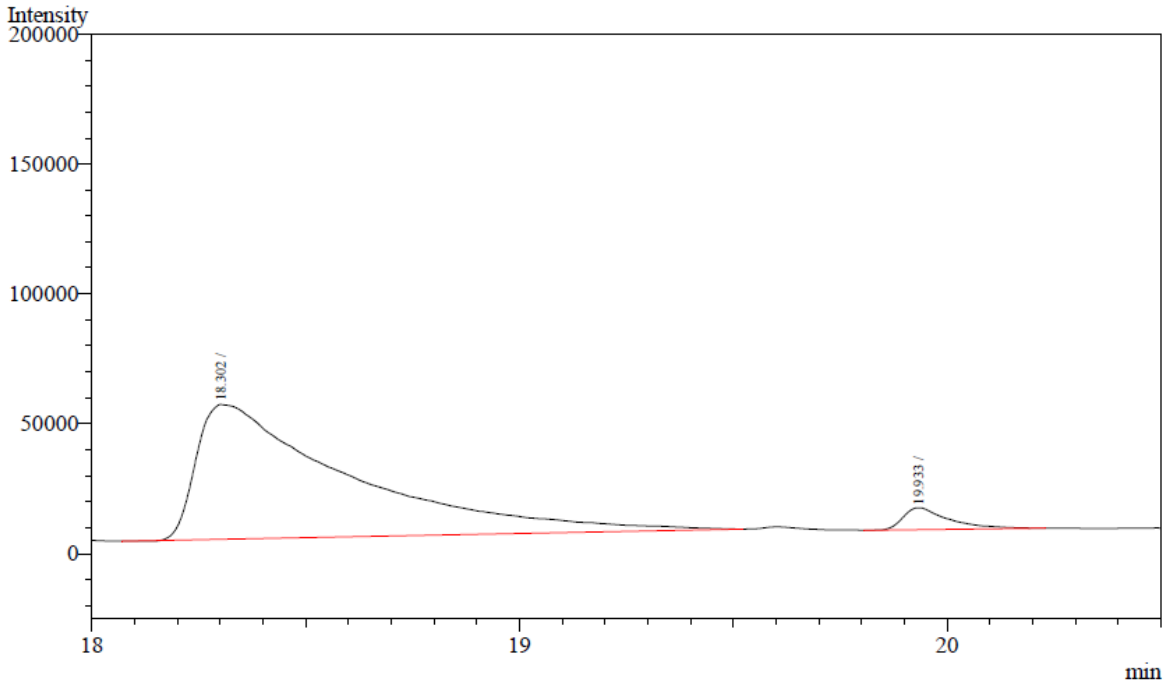


Chemical Formula: $C_{16}H_{28}O_2$
Exact Mass: 252.2089

Obtained as the mixture of cross-coupling products (138 mg pale yellow oil, 55% yield, 94:6) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	18.302	1279297	51893	95.396	95.3960
2	19.933	61742	8433	4.604	4.6040
Total		1341039	60326	100.000	100.0000

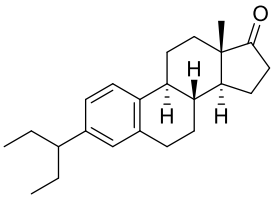
^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.22 (t, *J* = 3.7 Hz, 1H), 3.60 – 3.47 (m, 4H), 2.46 – 2.30 (m, 2H), 1.98 – 1.87 (m, 4H), 1.79 – 1.67 (m, 1H), 1.38 – 1.30 (m, 2H), 1.30 – 1.24 (m, 2H), 1.02 (s, 3H), 0.93 (s, 3H), 0.77 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 139.0, 118.5, 97.7, 70.4, 50.7, 34.7, 30.4, 28.0, 26.2, 23.0, 22.8, 22.2, 12.3.

IR (neat): ν (cm^{-1}) 2955, 2865, 1463, 1362, 1247, 1113, 1039, 859.

GC-MS (EI) m/z for $C_{16}H_{28}O_2$ ($[M]^{+\bullet}$): 252.

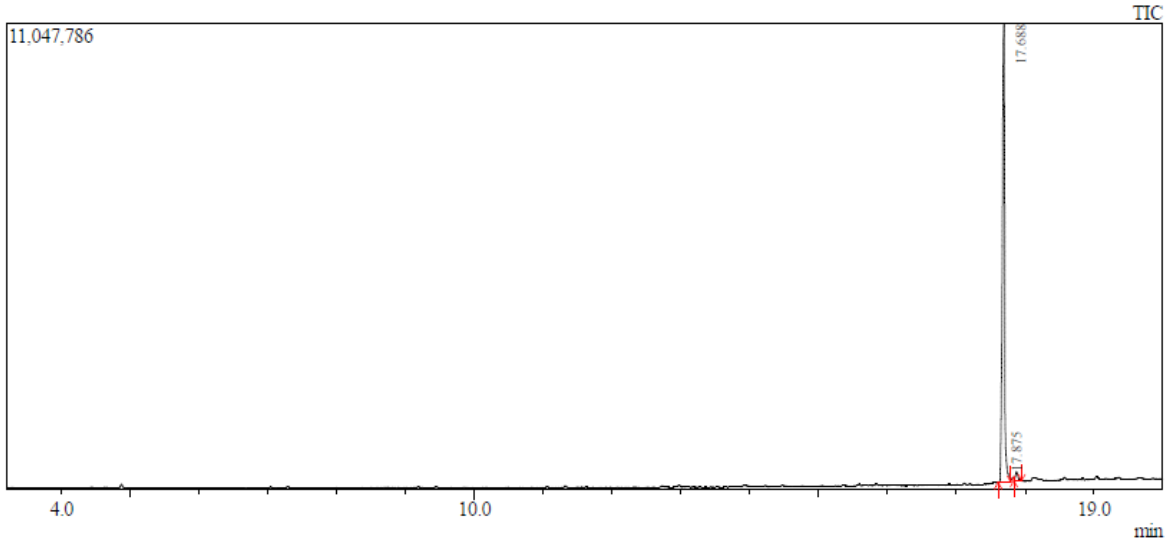
13-methyl-3-(pentan-3-yl)-6,7,8,9,11,12,13,14,15,16-decahydro-17H-cyclopenta[a]phenanthren-17-one 3-10r

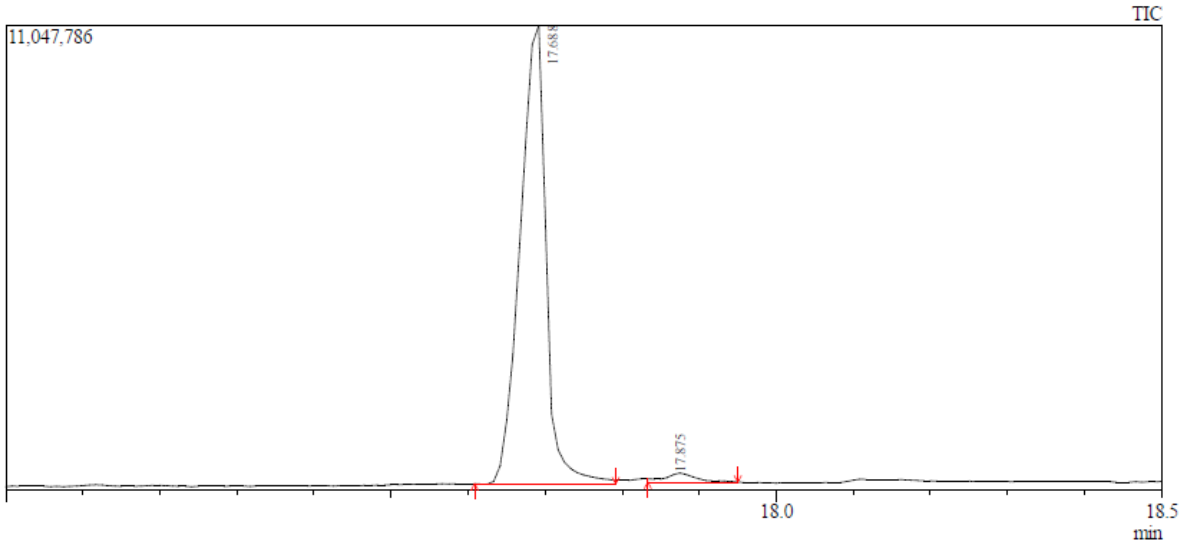


Chemical Formula: $C_{23}H_{32}O$
Exact Mass: 324.2453

Obtained as the mixture of cross-coupling products (263 mg white solid, 81% yield, 98:2) according to the **general procedure F**.

GC-MS trace of the crude mixture using L^{13} as the ligand

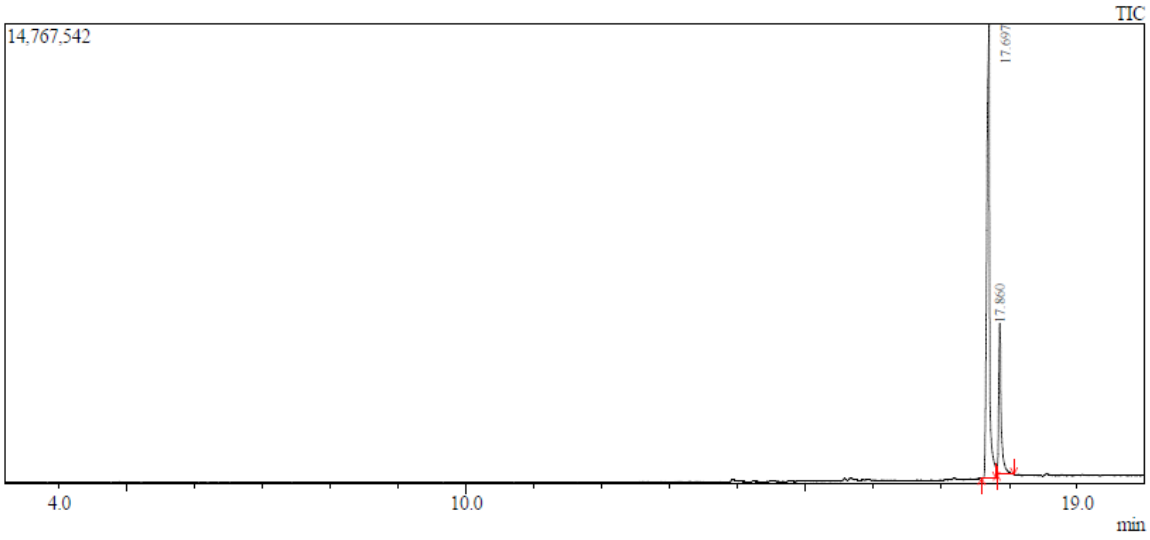


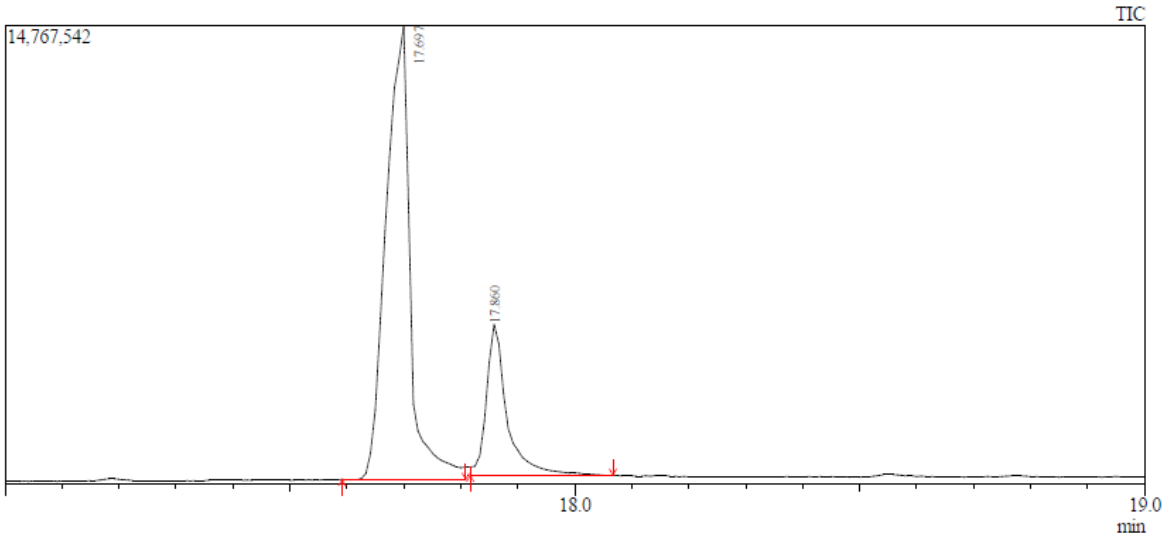


Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.688	17.608	17.792	25496649	97.78	10879366	98.08	2.34	MI	
2	17.875	17.833	17.950	579228	2.22	212565	1.92	2.72	MI	
				26075877	100.00	11091931	100.00			

GC-MS trace of the crude mixture using CPhos as the ligand





Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.697	17.592	17.808	43419695	78.15	14600559	75.05	2.97	MI	
2	17.860	17.817	18.067	12136420	21.85	4854670	24.95	2.50	MI	
				55556115	100.00	19455229	100.00			

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.25 – 7.18 (m, 1H), 6.98 – 6.91 (m, 1H), 6.90 – 6.85 (m, 1H), 3.03 – 2.86 (m, 2H), 2.52 (dd, *J* = 18.5, 8.6 Hz, 1H), 2.47 – 2.41 (m, 1H), 2.38 – 2.24 (m, 2H), 2.22 – 2.13 (m, 1H), 2.11 – 1.97 (m, 3H), 1.73 – 1.48 (m, 10H), 0.94 (s, 3H), 0.82 (t, *J* = 7.4 Hz, 6H).

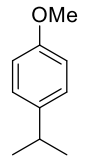
^{13}C NMR (101 MHz, $CDCl_3$) δ 220.7, 143.2, 136.9, 135.9, 128.4, 125.1, 125.0, 50.6, 49.1, 48.0, 44.4, 38.3, 35.9, 31.7, 29.5, 29.1, 26.7, 25.7, 21.6, 13.9, 12.3.

IR (neat): ν (cm^{-1}) 2928, 2870, 1737, 1455, 1264, 1007, 821, 735.

HRMS (ESI): Calcd for $C_{23}H_{32}NaO$ $[M+Na]^+$: 347.2345, found: 347.2347.

m.p.: 112-115 ^{o}C.

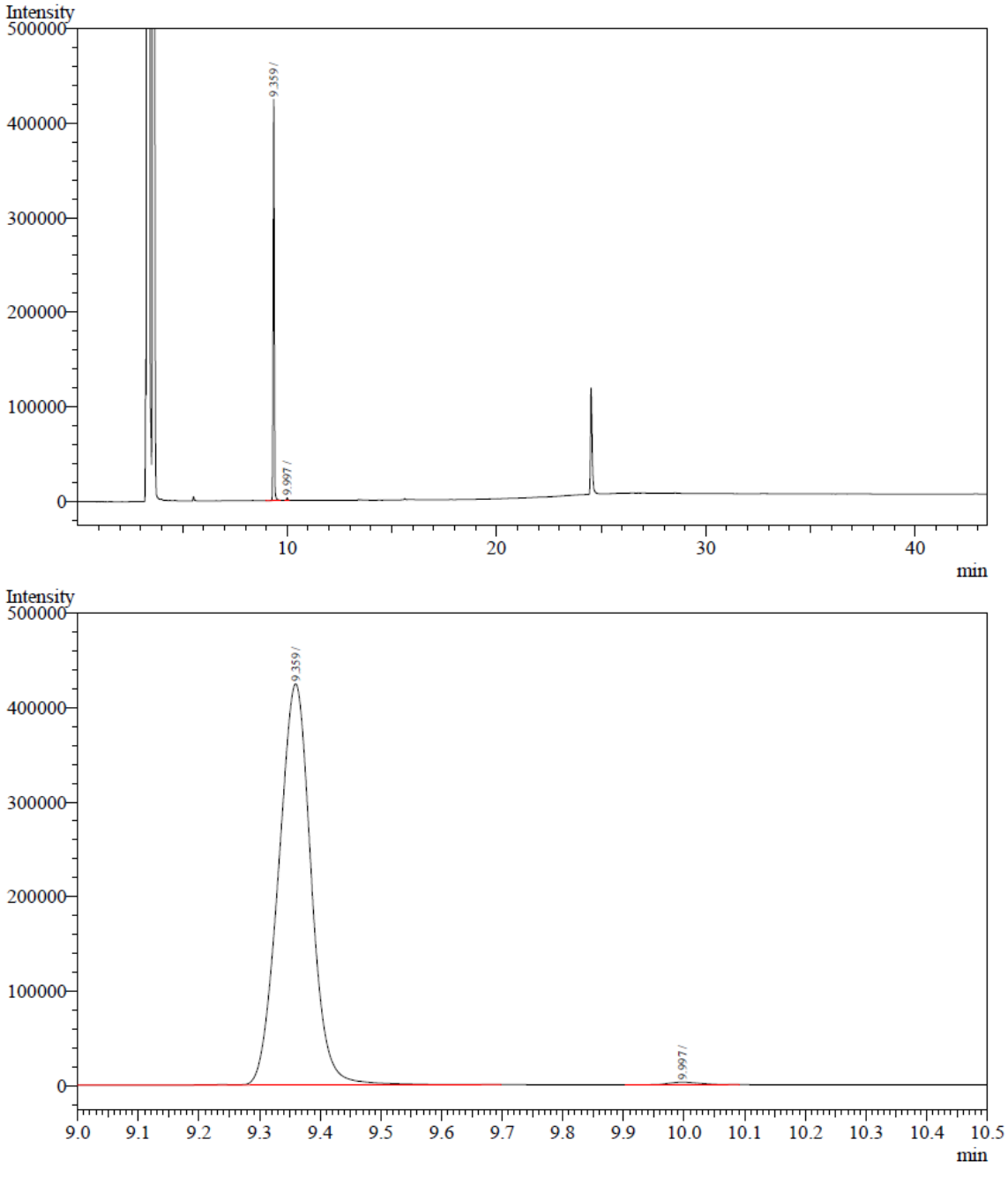
1-isopropyl-4-methoxybenzene 3-21a



Chemical Formula: $C_{10}H_{14}O$
Exact Mass: 150.1045

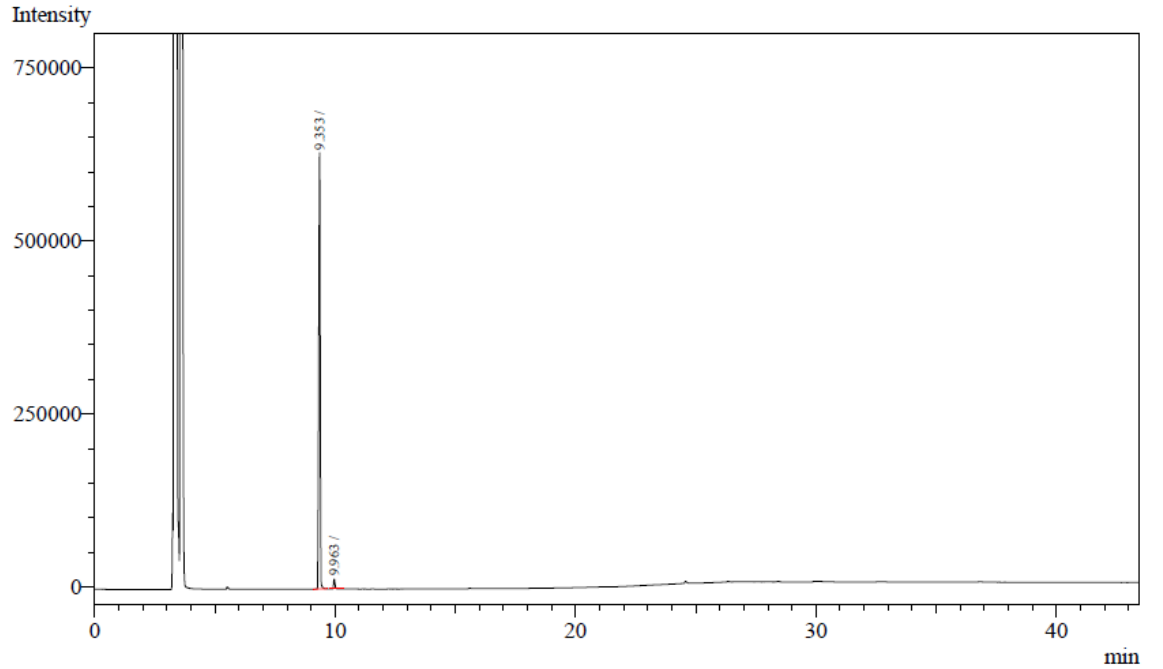
Obtained as the mixture of cross-coupling products (82.5 mg colourless oil, 60% yield, 99:1) according to the **general procedure F**.

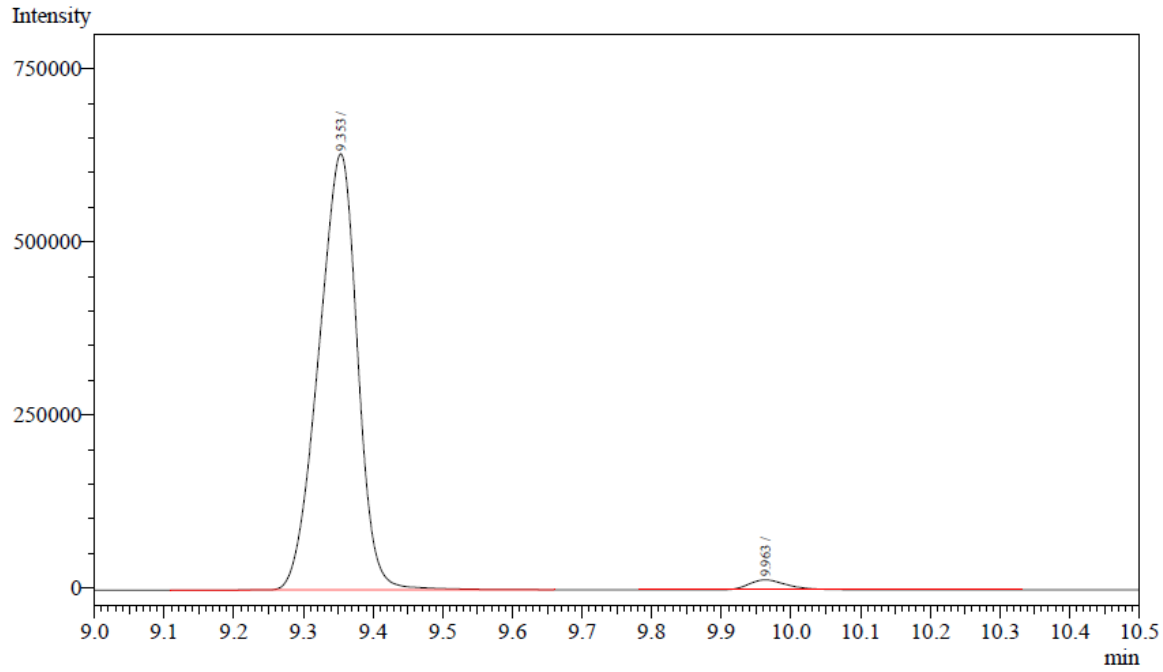
GC trace of the crude mixture using L^{13} as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	9.359	1573672	423102	99.360	99.3601
2	9.997	10134	2664	0.640	0.6399
Total		1583806	425766	100.000	100.0000

GC trace of the crude mixture using CPhos as the ligand





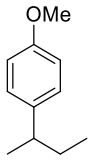
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	9.353	2443684	628378	97.791	97.7915
2	9.963	55189	14078	2.209	2.2085
Total		2498873	642456	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.21 – 7.12 (m, 2H), 6.88 – 6.78 (m, 2H), 3.80 (s, 3H), 2.87 (hept, *J* = 6.9 Hz, 1H), 1.24 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 141.2, 127.4, 113.8, 55.4, 33.4, 24.4.

The NMR data for this compound was consistent with literature data.[29a]

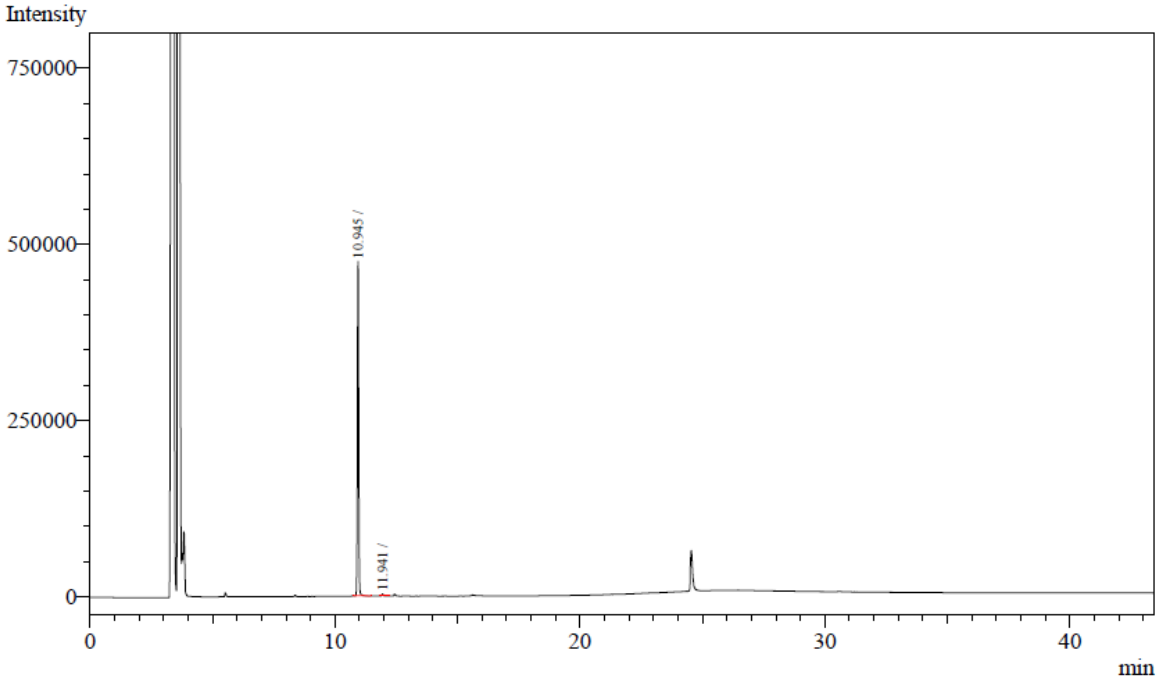
1-(*sec*-butyl)-4-methoxybenzene 3-21b

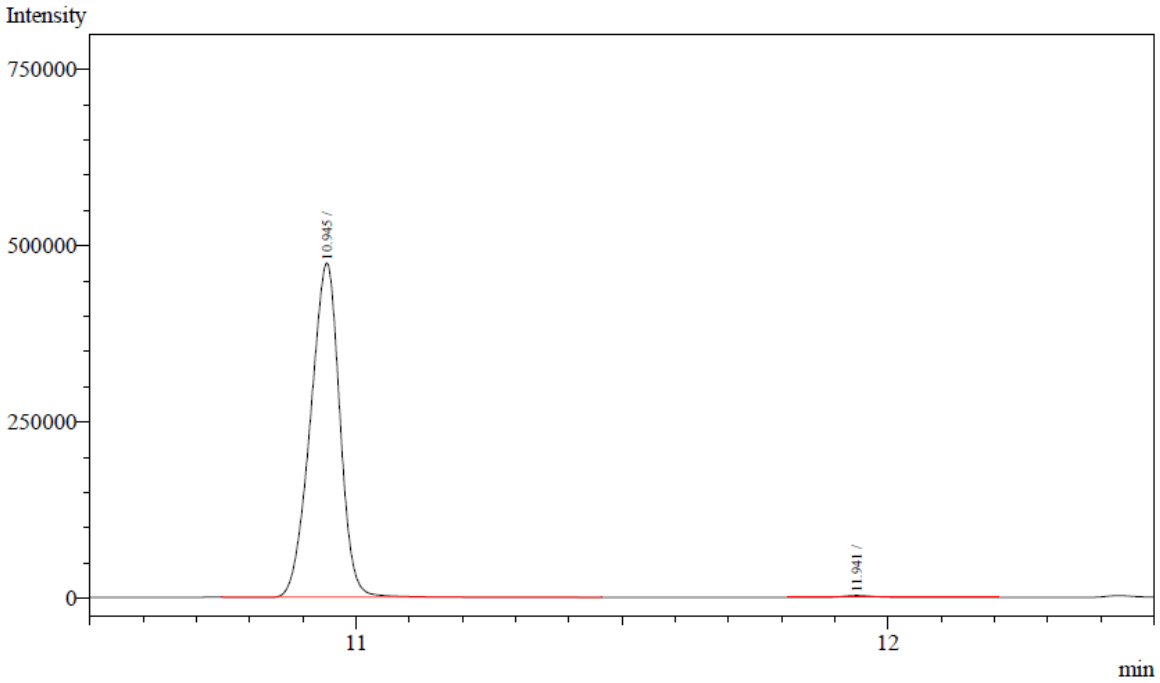


Chemical Formula: $C_{11}H_{16}O$
Exact Mass: 164.1201

Obtained as the mixture of cross-coupling products (102 mg colourless oil, 62% yield, >99:1) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





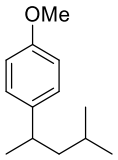
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	10.945	1812123	473077	99.398	99.3980
2	11.941	10975	2611	0.602	0.6020
Total		1823098	475688	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.07 (m, 2H), 6.88 – 6.81 (m, 2H), 3.80 (s, 3H), 2.63 – 2.49 (m, 1H), 1.61 – 1.53 (m, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.82 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 140.0, 128.0, 113.8, 55.4, 41.0, 31.5, 22.2, 12.4.

The NMR data for this compound was consistent with literature data.[154]

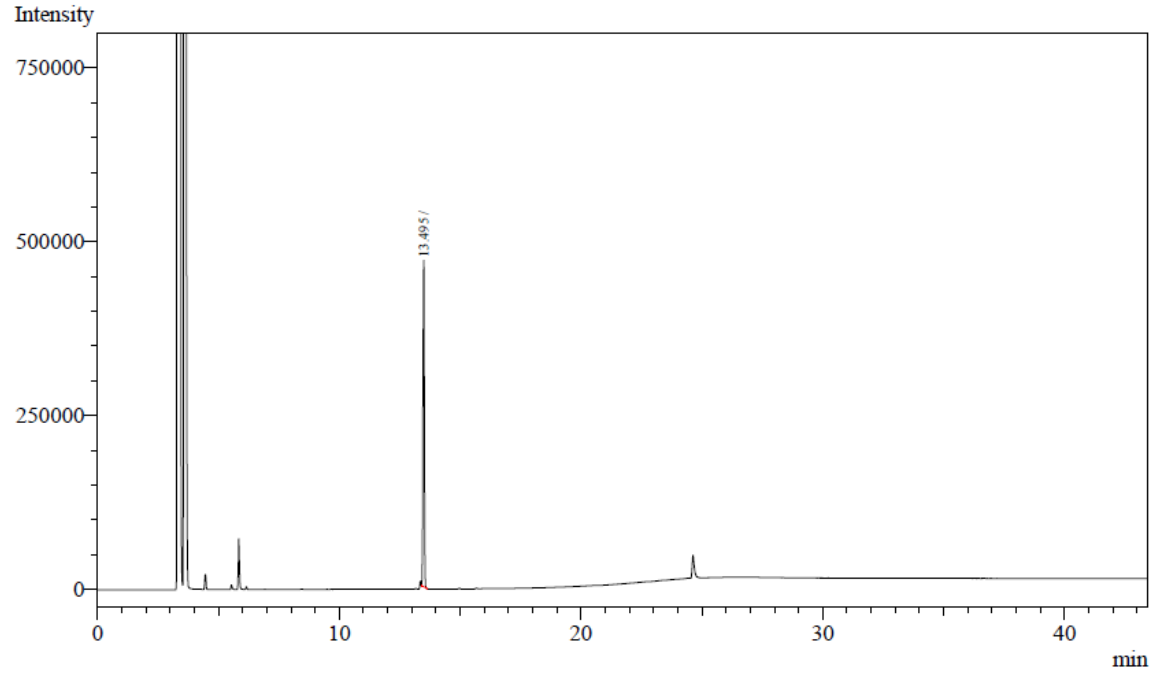
1-methoxy-4-(4-methylpentan-2-yl)benzene 3-21c

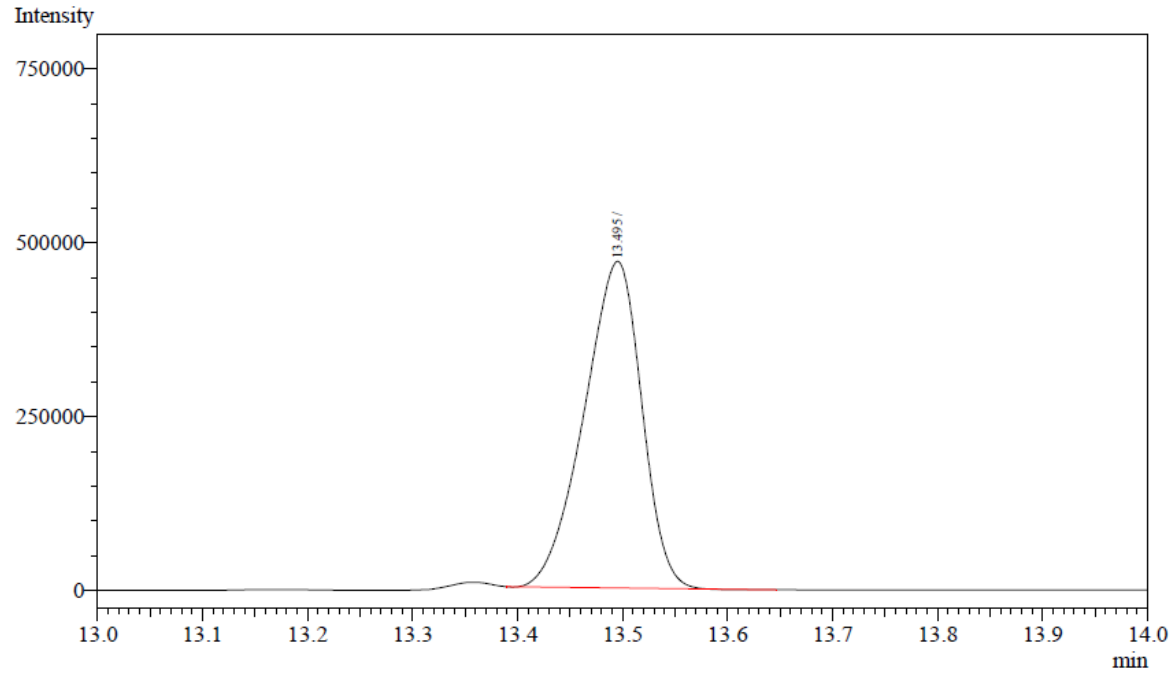


Chemical Formula: $C_{13}H_{20}O$
Exact Mass: 192.1514

Obtained as the mixture of cross-coupling products (146 mg colourless oil, 76% yield, >99:1) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	13.495	1791441	468650	100.000	100.0000
Total		1791441	468650	100.000	100.0000

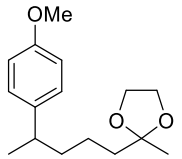
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.09 (m, 2H), 6.87 – 6.80 (m, 2H), 3.80 (s, 3H), 2.81 – 2.68 (m, 1H), 1.51 – 1.34 (m, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.2 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 140.3, 127.9, 113.8, 55.4, 48.1, 36.8, 25.7, 23.2, 23.1, 22.5.

IR (neat): ν (cm^{-1}) 2955, 1612, 1512, 1464, 1297, 1246, 1178, 1039, 830, 690.

HRMS (ESI): Calcd for $C_{13}H_{20}NaO$ $[M+Na]^+$: 215.1406, found: 215.1409.

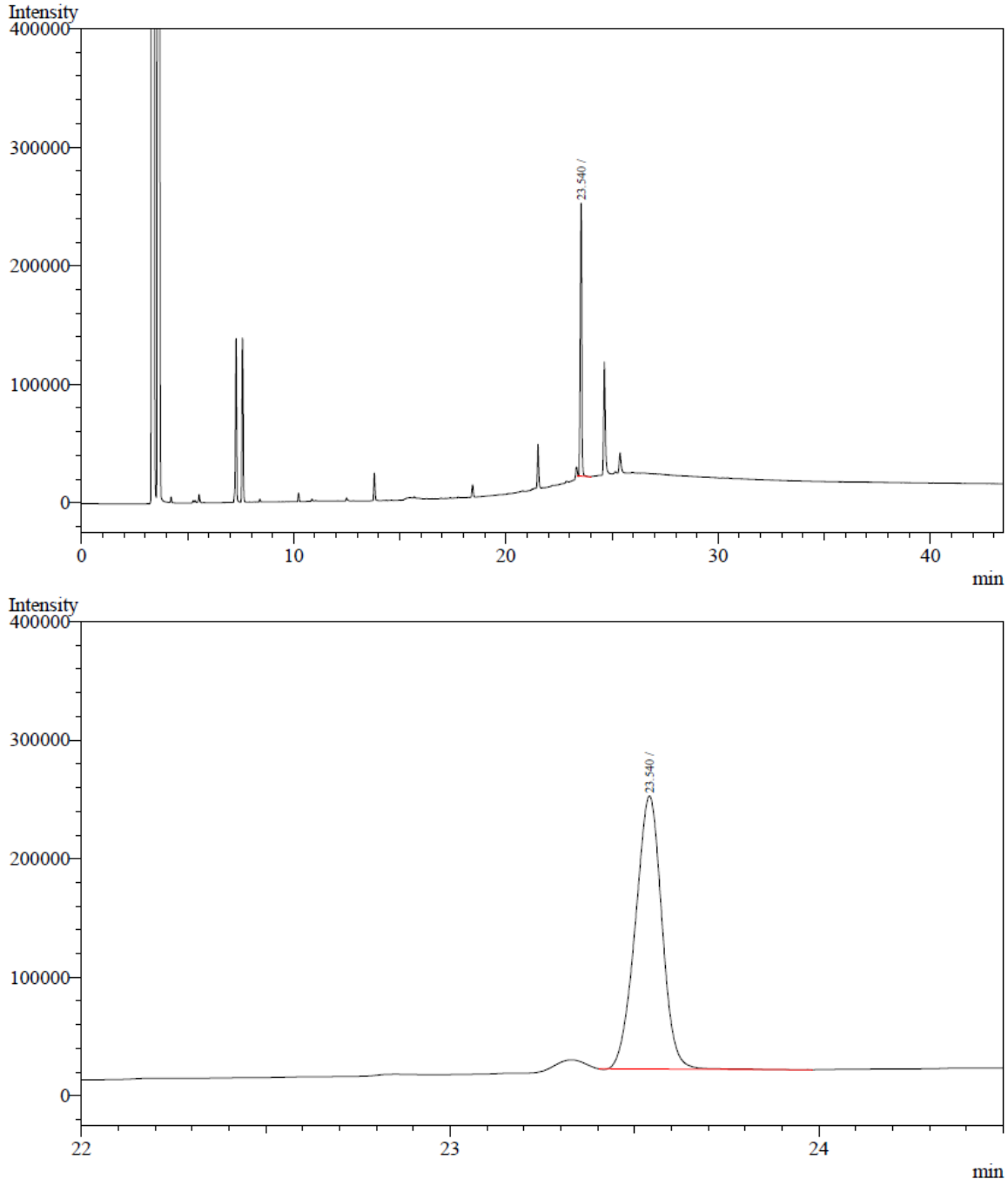
2-(4-(4-methoxyphenyl)pentyl)-2-methyl-1,3-dioxolane 3-21d



Chemical Formula: $C_{16}H_{24}O_3$
Exact Mass: 264.1725

Obtained as the mixture of cross-coupling products (152 mg colourless oil, 58% yield, >99:1) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	23.540	1149379	229871	100.000	100.0000
Total		1149379	229871	100.000	100.0000

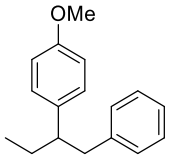
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.13 – 7.05 (m, 2H), 6.87 – 6.77 (m, 2H), 3.94 – 3.85 (m, 4H), 3.79 (s, 3H), 2.74 – 2.54 (m, 1H), 1.64 – 1.58 (m, 2H), 1.57 – 1.50 (m, 2H), 1.39 – 1.29 (m, 2H), 1.26 (s, 3H), 1.21 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 140.0, 127.9, 113.8, 110.3, 64.7, 64.7, 55.4, 39.3, 39.2, 39.0, 23.8, 22.5, 22.4.

IR (neat): ν (cm^{-1}) 2362, 2313, 2194, 2100, 2047, 1996, 1947, 1866, 1697, 1207, 1149, 1088, 831, 740, 680.

HRMS (ESI): Calcd for $C_{16}H_{24}NaO_3$ $[M+Na]^+$: 287.1618, found: 287.1620.

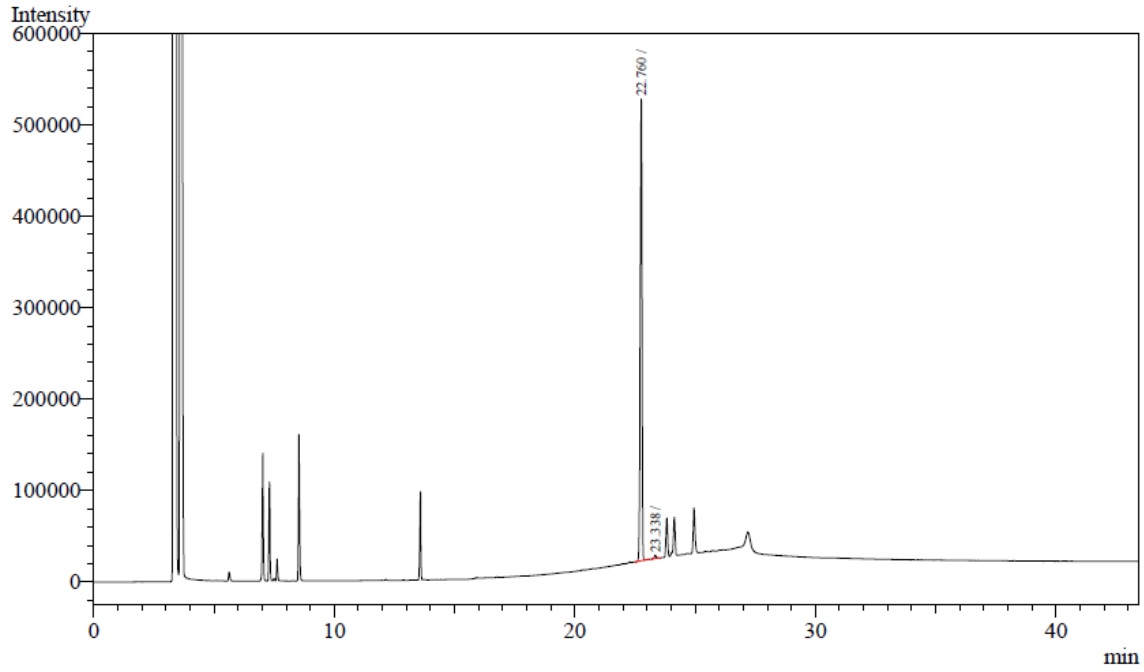
1-methoxy-4-(1-phenylbutan-2-yl)benzene 3-21e

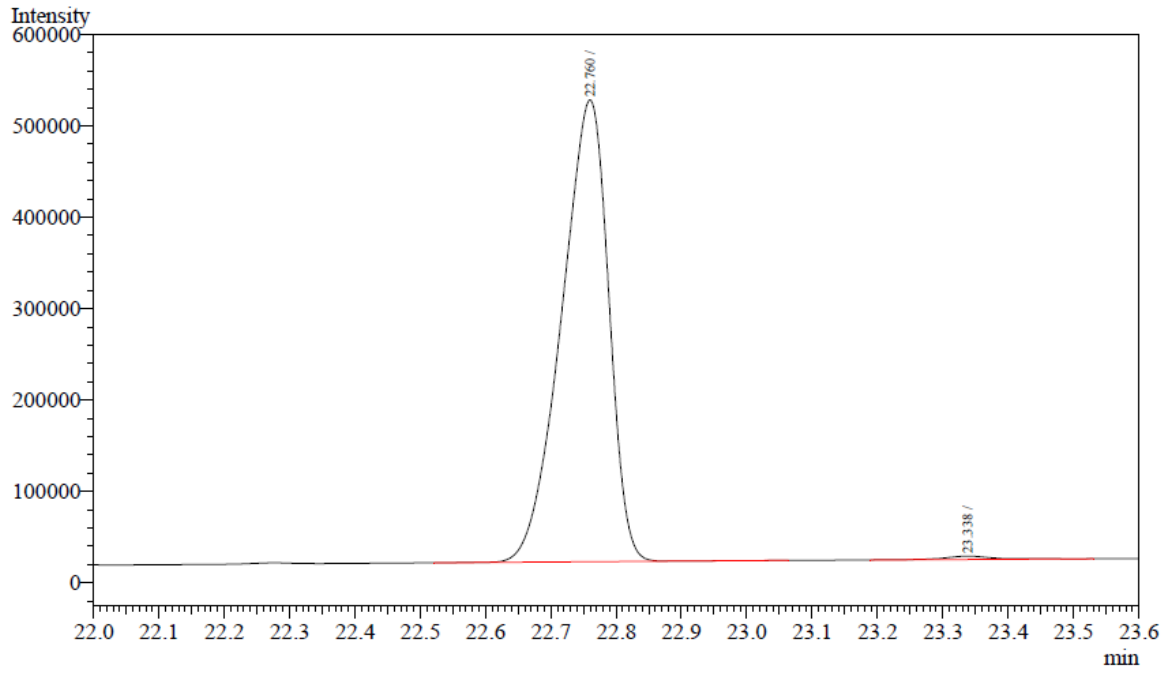


Chemical Formula: $C_{17}H_{20}O$
Exact Mass: 240.1514

Obtained as the mixture of cross-coupling products (144 mg colourless oil, 60% yield, >99:1) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	22.760	2532502	503930	99.244	99.2437
2	23.338	19300	3578	0.756	0.7563
Total		2551802	507508	100.000	100.0000

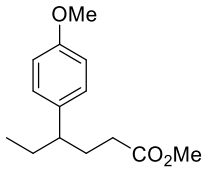
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.24 – 7.19 (m, 2H), 7.18 – 7.12 (m, 1H), 7.07 – 7.01 (m, 4H), 6.85 – 6.80 (m, 2H), 3.79 (s, 3H), 2.92 – 2.82 (m, 2H), 2.74 – 2.64 (m, 1H), 1.80 – 1.66 (m, 1H), 1.64 – 1.52 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, CDCl3) δ 157.9, 141.1, 137.2, 129.3, 128.8, 128.1, 125.8, 113.7, 55.3, 49.1, 43.8, 28.6, 12.3.

IR (neat): ν (cm^{-1}) 2926, 1611, 1511, 1455, 1300, 1247, 1177, 1035, 829, 748, 699.

HRMS (ESI): Calcd for $C_{17}H_{20}NaO$ $[M+Na]^+$: 263.1406, found: 263.1408.

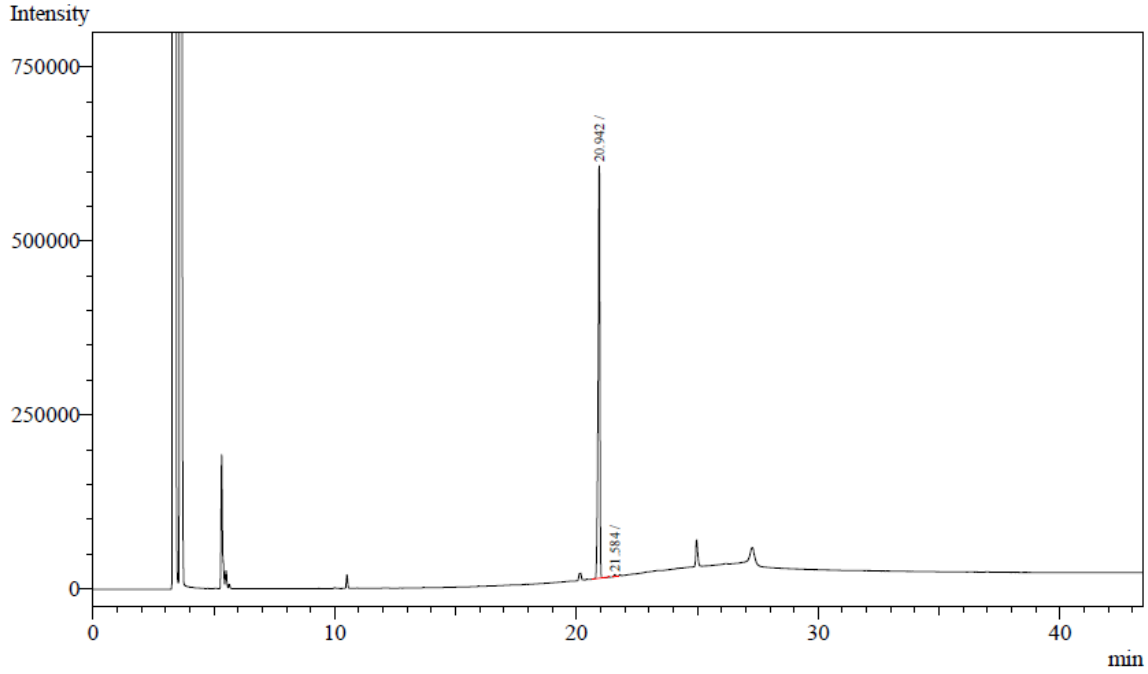
<u>methyl 4-(4-methoxyphenyl)hexanoate 3-21f</u>

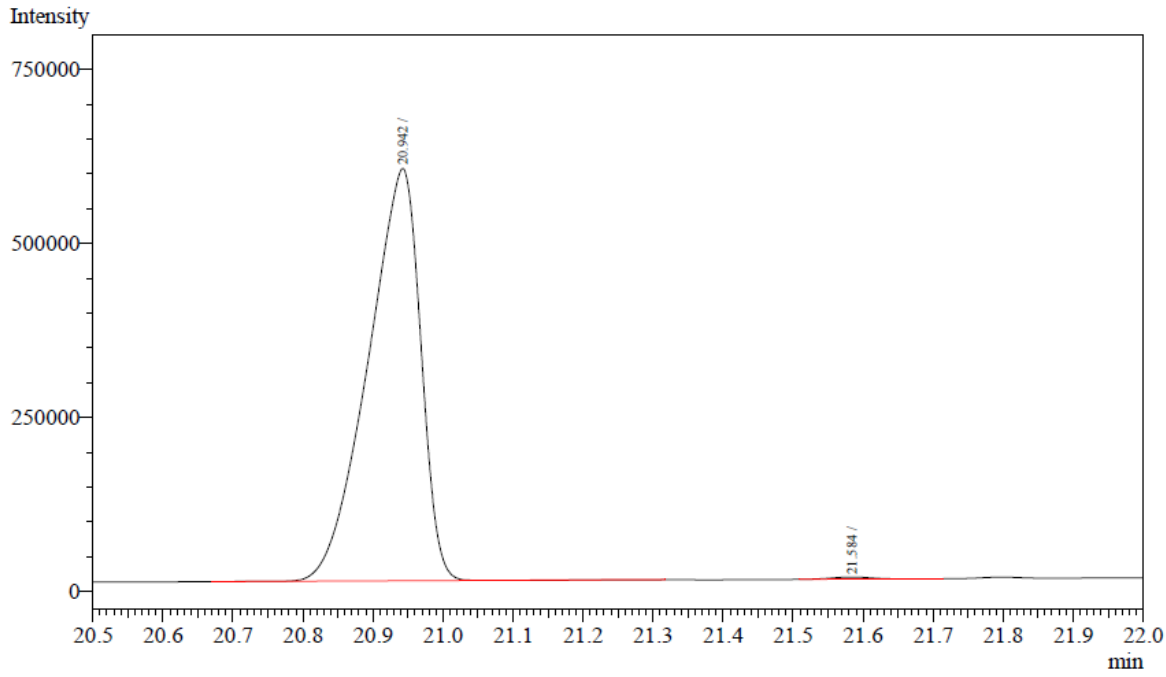


Chemical Formula: $C_{14}H_{20}O_3$
Exact Mass: 236.1412

Obtained as the mixture of cross-coupling products (195 mg colourless oil, 83% yield, >99:1) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.942	3082128	591783	99.652	99.6520
2	21.584	10763	2711	0.348	0.3480
Total		3092891	594494	100.000	100.0000

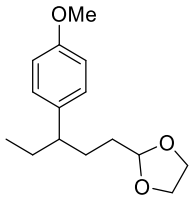
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.07 – 7.00 (m, 2H), 6.88 – 6.80 (m, 2H), 3.79 (s, 3H), 3.61 (s, 3H), 2.42 – 2.32 (m, 1H), 2.17 – 2.10 (m, 2H), 2.05 – 1.95 (m, 1H), 1.85 – 1.74 (m, 1H), 1.71 – 1.59 (m, 1H), 1.58 – 1.48 (m, 1H), 0.77 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 158.1, 136.5, 128.7, 113.9, 55.3, 51.5, 46.6, 32.4, 31.7, 29.9, 12.2.

IR (neat): ν (cm^{-1}) 2956, 1736, 1611, 1512, 1458, 1302, 1246, 1162, 1034, 829, 680.

HRMS (ESI): Calcd for $C_{14}H_{20}NaO_3$ $[M+Na]^+$: 259.1305, found: 259.1306.

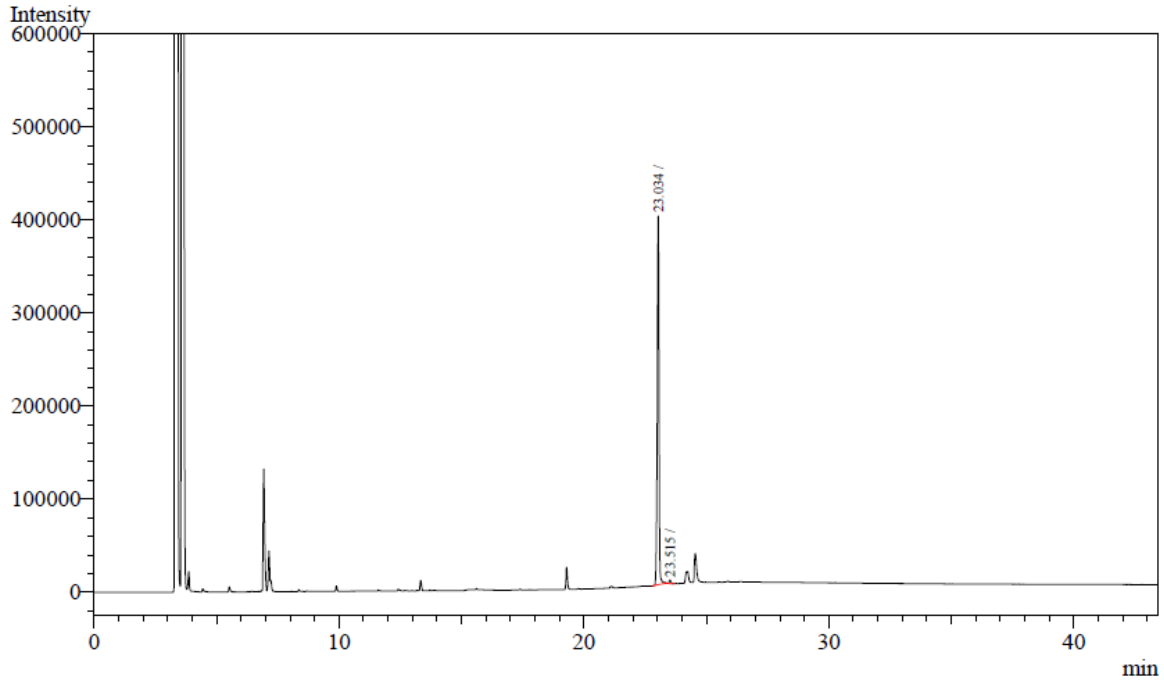
2-(3-(4-methoxyphenyl)pentyl)-1,3-dioxolane 3-21g

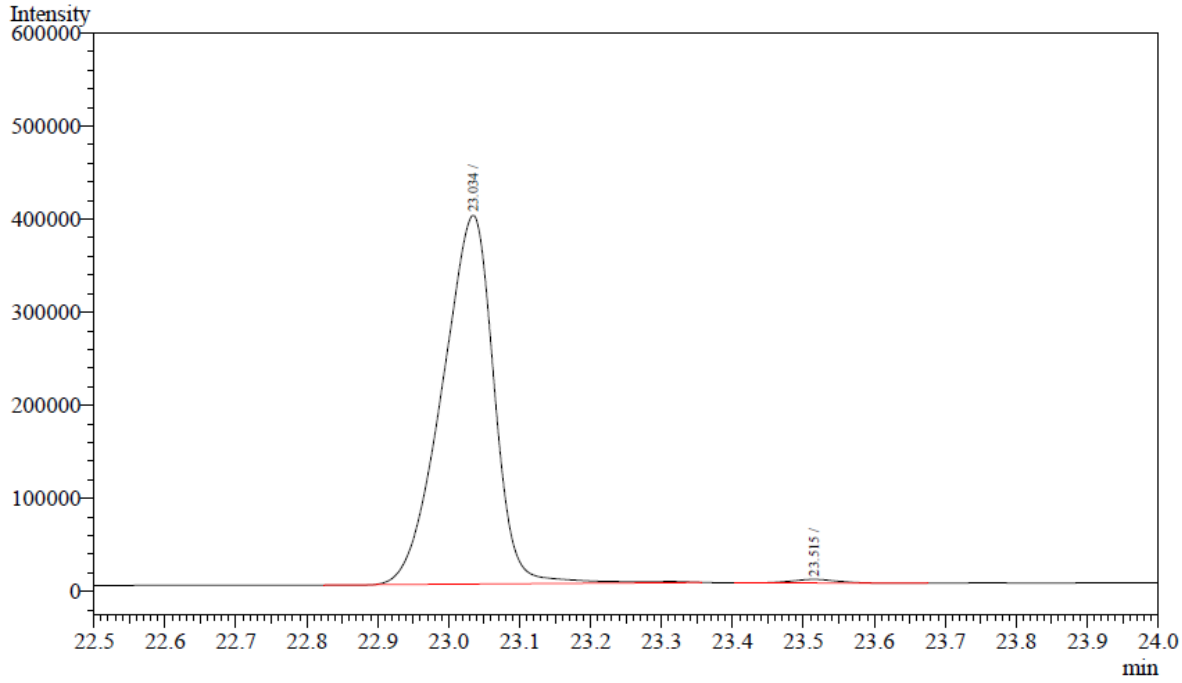


Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250.1569

Obtained as the mixture of cross-coupling products (185 mg colourless oil, 74% yield, 99:1) according to the **general procedure F**.

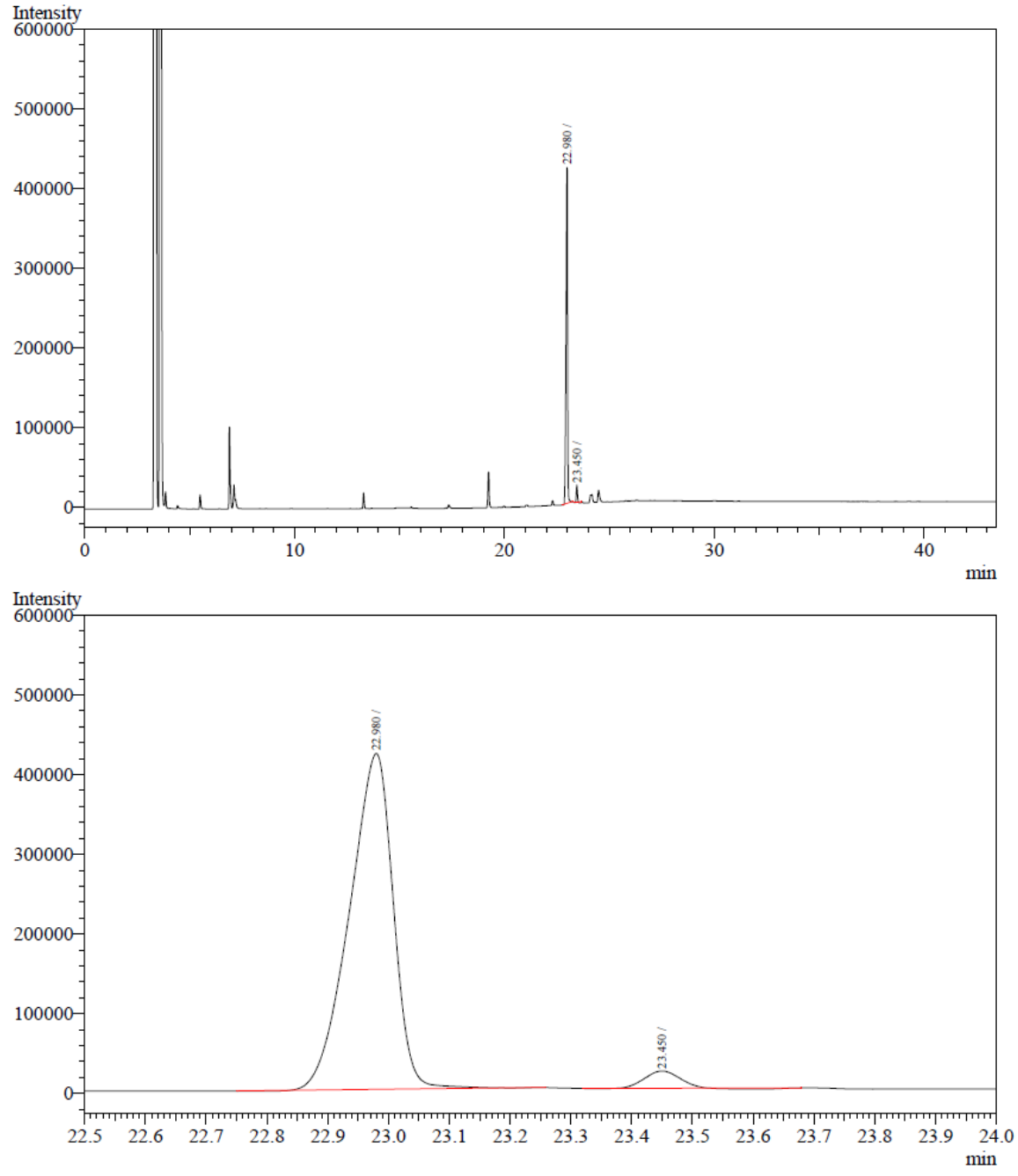
GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	23.034	2018390	395402	99.203	99.2029
2	23.515	16217	3819	0.797	0.7971
Total		2034607	399221	100.000	100.0000

GC trace of the crude mixture with CPhos as the ligand



Peak#	Ret.Time	Area	Height	Conc.	Area%
1	22.980	2112436	419353	96.368	96.3676
2	23.450	79625	21670	3.632	3.6324
Total		2192061	441023	100.000	100.0000

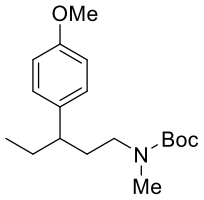
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.10 – 7.01 (m, 2H), 6.87 – 6.77 (m, 2H), 4.78 (t, *J* = 4.6 Hz, 1H), 3.97 – 3.80 (m, 4H), 3.78 (s, 3H), 2.48 – 2.30 (m, 1H), 1.85 – 1.72 (m, 1H), 1.68 – 1.61 (m, 1H), 1.59 – 1.45 (m, 4H), 0.76 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 137.4, 128.7, 113.8, 104.8, 65.0, 64.9, 55.4, 47.0, 32.2, 30.9, 30.0, 12.3.

IR (neat): ν (cm^{-1}) 2955, 2873, 1611, 1511, 1460, 1408, 1300, 1246, 1140, 1034, 943, 909, 830, 682.

HRMS (ESI): Calcd for $C_{15}H_{22}NaO_3$ $[M+Na]^+$: 273.1461, found: 273.1458.

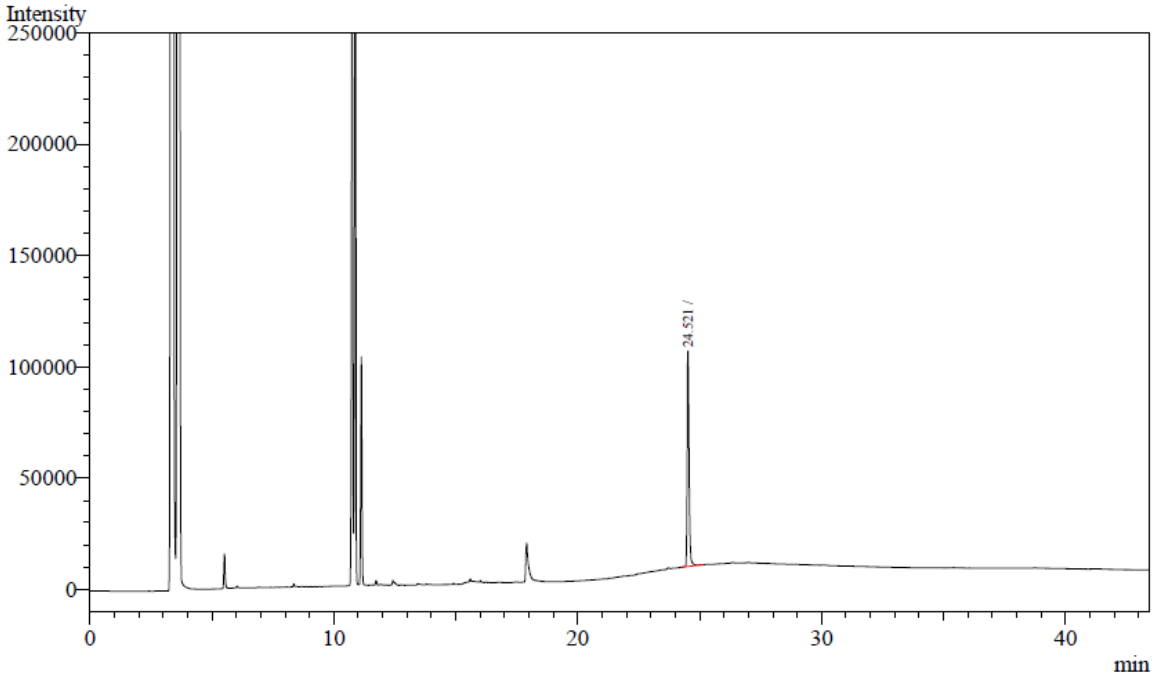
***tert*-butyl (3-(4-methoxyphenyl)pentyl)(methyl)carbamate 3-21h**

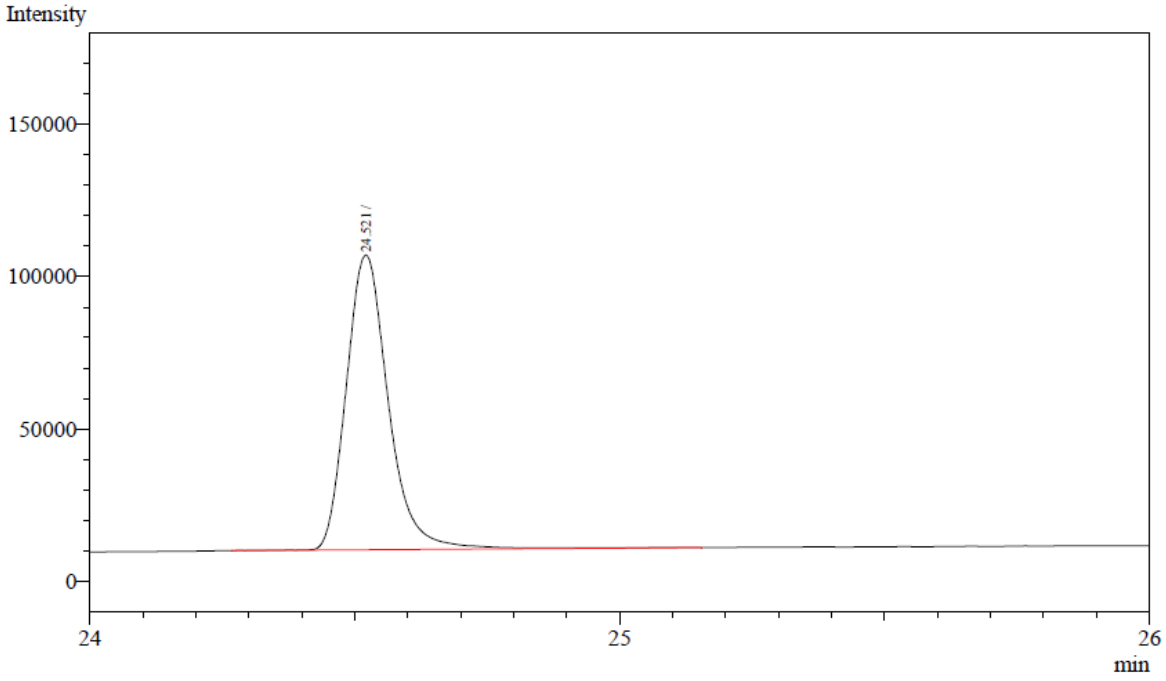


Chemical Formula: $C_{18}H_{29}NO_3$
Exact Mass: 307.2147

Obtained as the mixture of cross-coupling products (185 mg colourless oil, 60% yield, 99:1) according to the **general procedure F** with a modified conditions (Using 2.0 equiv alkyl bromide/Mg/LiCl,$ZnCl_2$, 5 mol% Pd_2dba_3, 10 mol% **L[13]**, at 60 °C).

GC trace of the crude mixture with L[13] as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	24.521	536011	96615	100.000	100.0000
Total		536011	96615	100.000	100.0000

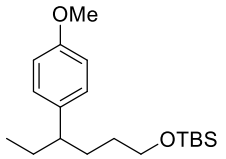
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.10 – 7.02 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 3.27 – 2.89 (m, 2H), 2.76 (s, 3H), 2.34 (s, 1H), 1.89 – 1.79 (m, 1H), 1.77 – 1.63 (m, 2H), 1.57 – 1.46 (m, 1H), 1.42 (s, 9H), 0.76 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 158.0, 155.9, 137.1, 128.5, 113.9, 79.2, 55.4, 47.7, 44.6, 34.4, 30.5, 30.1, 28.6, 12.2.

IR (neat): ν (cm^{-1}) 2930, 1694, 1612, 1512, 1460, 1394, 1249, 1175, 1037, 879, 830, 772.

HRMS (ESI): Calcd for $C_{18}H_{29}NNaO_3$ $[M+Na]^+$: 330.2040, found: 330.2039.

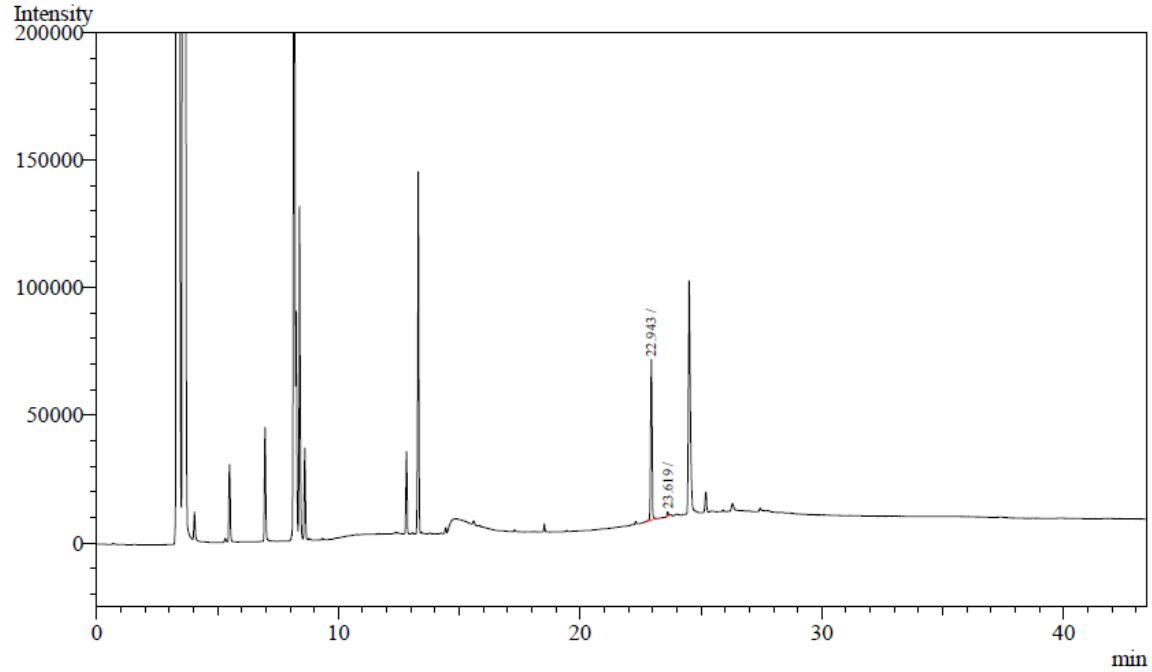
***tert*-butyl((4-(4-methoxyphenyl)hexyl)oxy)dimethylsilane 3-21i**

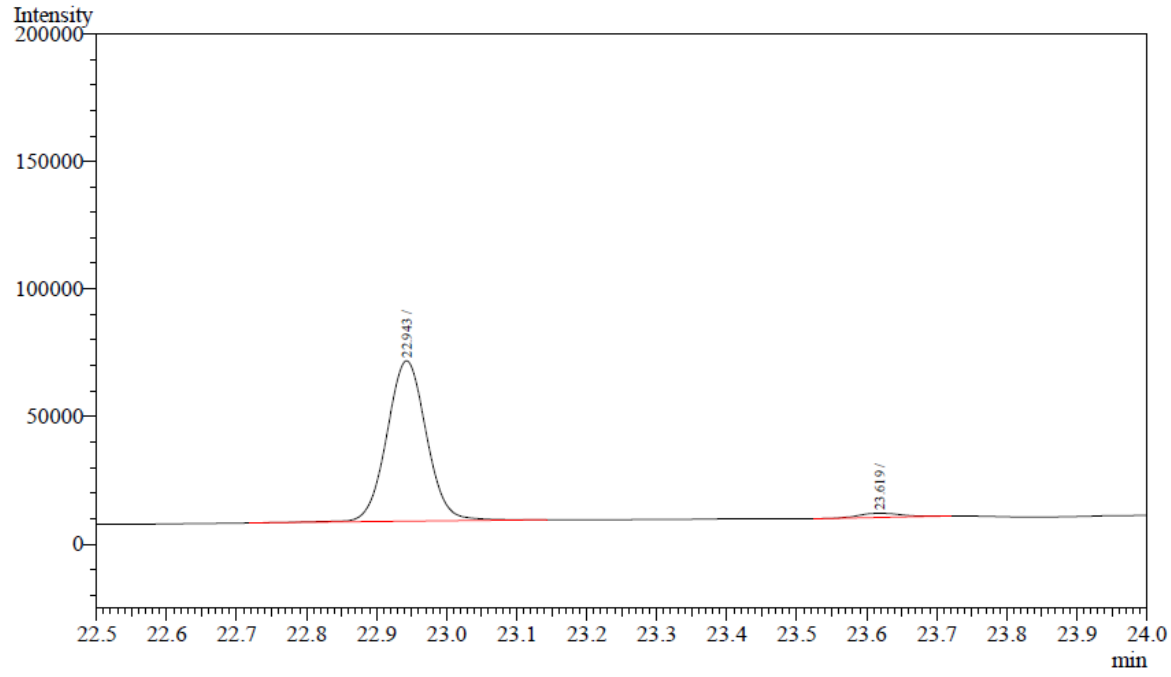


Chemical Formula: $C_{19}H_{34}O_2Si$
Exact Mass: 322.2328

Obtained as the mixture of cross-coupling products (196 mg colourless oil, 63% yield, 97:3) according to the **general procedure F**.

GC trace of the crude mixture with L^{13} as the ligand





Peak#	Ret.Time	Area	Height	Conc.	Area%
1	22.943	248007	62736	97.298	97.2976
2	23.619	6888	1685	2.702	2.7024
Total		254895	64421	100.000	100.0000

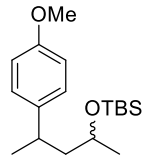
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.10 – 7.01 (m, 2H), 6.87 – 6.79 (m, 2H), 3.79 (s, 3H), 3.53 (t, *J* = 6.5 Hz, 2H), 2.42 – 2.28 (m, 1H), 1.74 – 1.60 (m, 2H), 1.55 – 1.47 (m, 2H), 1.40 – 1.32 (m, 2H), 0.88 (s, 9H), 0.76 (t, *J* = 7.4 Hz, 3H), 0.01 (s, 3H), 0.01 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.9, 138.0, 128.7, 113.7, 63.4, 55.4, 46.9, 32.8, 31.0, 30.1, 26.1, 18.5, 12.3, -5.1.

IR (neat): ν (cm^{-1}) 2930, 2858, 1612, 1512, 1463, 1249, 1178, 1098, 1040, 833, 776.

HRMS (ESI): Calcd for $C_{19}H_{35}O_2Si$ $[M+H]^+$: 323.2401, found: 323.2404.

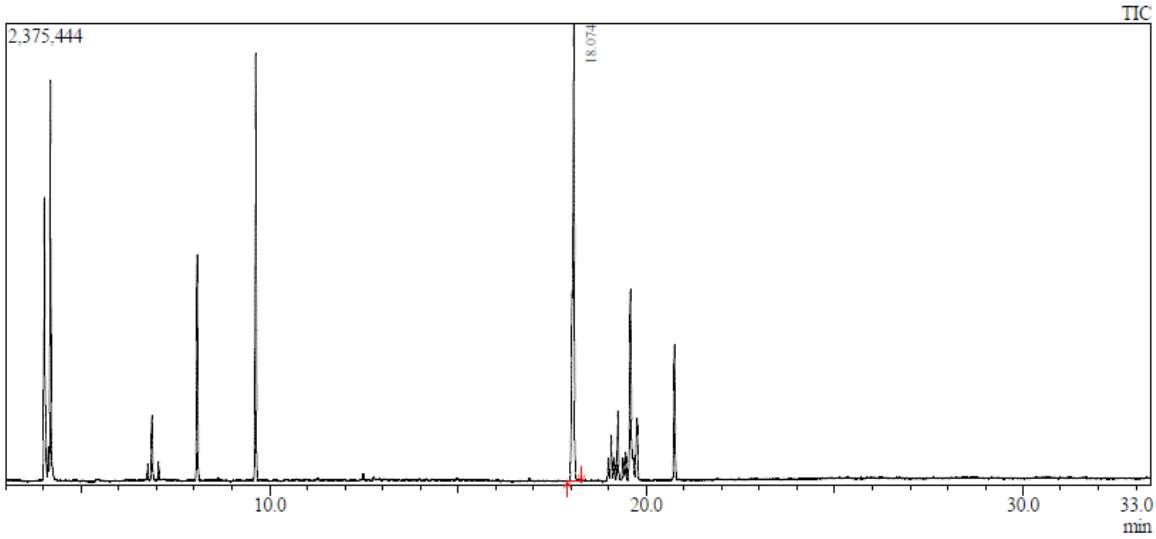
***tert*-butyl((4-(4-methoxyphenyl)pentan-2-yl)oxy)dimethylsilane 3-21j**

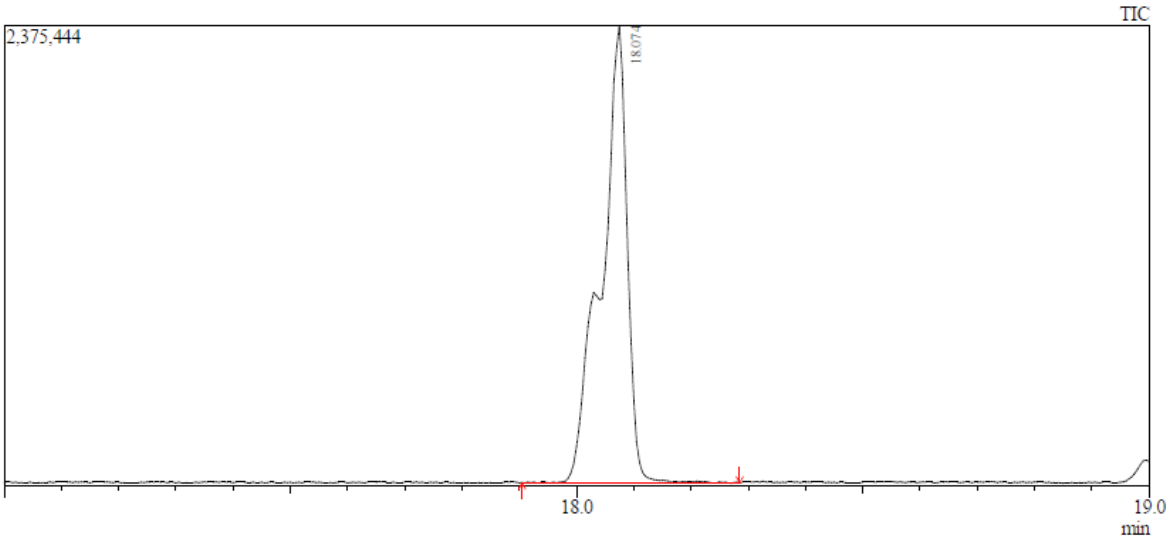


Chemical Formula: $C_{18}H_{32}O_2Si$
Exact Mass: 308.2172

Obtained as a mixture of diastereoisomers (160 mg colourless oil, 52% yield, >99:1 selectivity, 60:40 d.r.) according to the **general procedure F**.

GC-MS trace of the crude mixture with L^{13} as the ligand

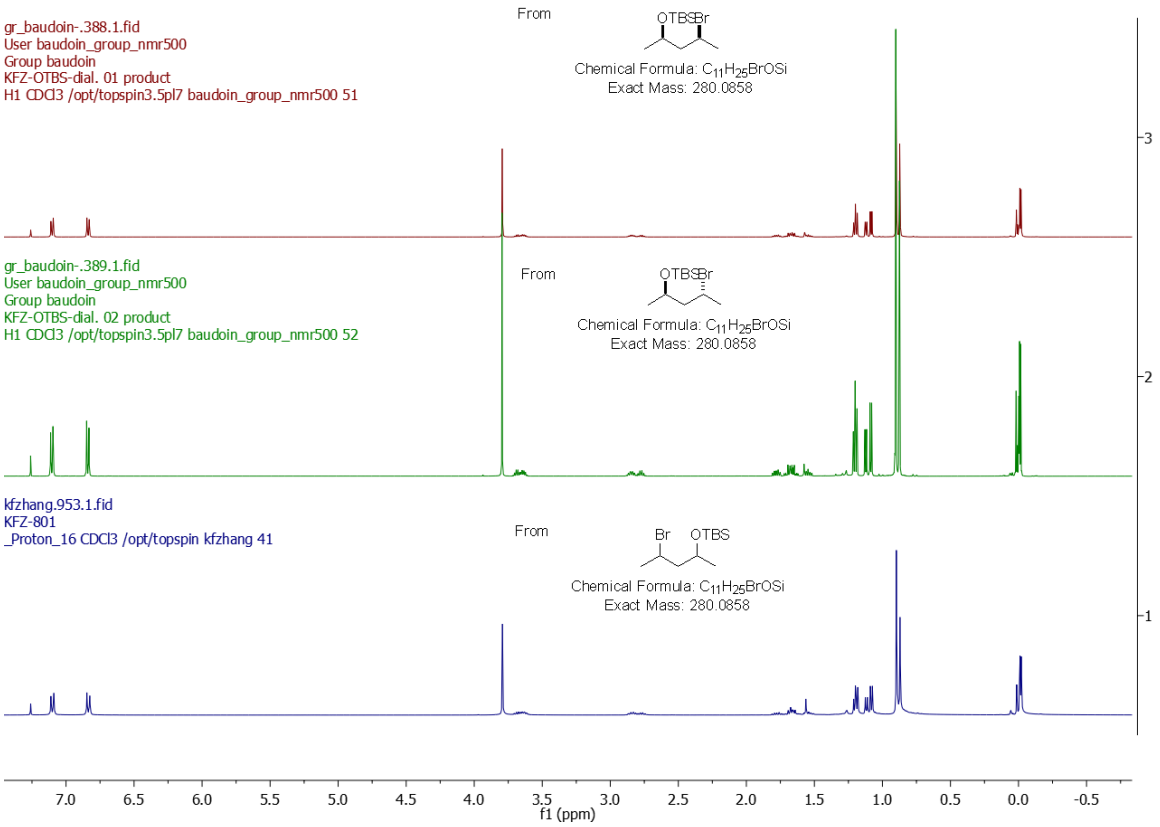




Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	18.074	17.905	18.285	7424638	100.00	2356213	100.00	3.15	MI	
				7424638	100.00	2356213	100.00			

The same result (d.r. 60:40) was obtained with isolated *syn* and *anti* diastereoisomers (determined by ^{1}H-NMR)



The data given below was the mixtures of diastereomers.

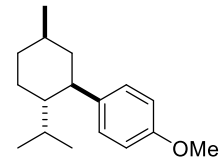
^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.15 – 7.06 (m, 2H), 6.89 – 6.79 (m, 2H), 3.79 (s, 3H), 3.71 – 3.59 (m, 1H), 2.90 – 2.73 (m, 1H), 1.82 – 1.60 (m, 2H), 1.20 (dd, *J* = 6.9, 5.2 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 1H), 1.08 (d, *J* = 6.1 Hz, 2H), 0.88 (d, *J* = 10.8 Hz, 9H), 0.03 – -0.10 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 157.9, 157.8, 140.0, 139.8, 128.1, 127.8, 113.9, 113.8, 67.0, 66.7, 55.4, 55.4, 48.8, 48.6, 35.8, 35.5, 26.2, 26.1, 24.5, 23.9, 23.9, 22.5, 18.3, 18.3, -3.8, -4.2, -4.4, -4.6.

IR (neat): ν (cm^{-1}) 2956, 1613, 1513, 1462, 1373, 1296, 1248, 1144, 1041, 830, 774, 720.

HRMS (ESI): Calcd for $C_{18}H_{32}NaO_2Si$ $[M+Na]^+$: 331.2064, found: 331.2060.

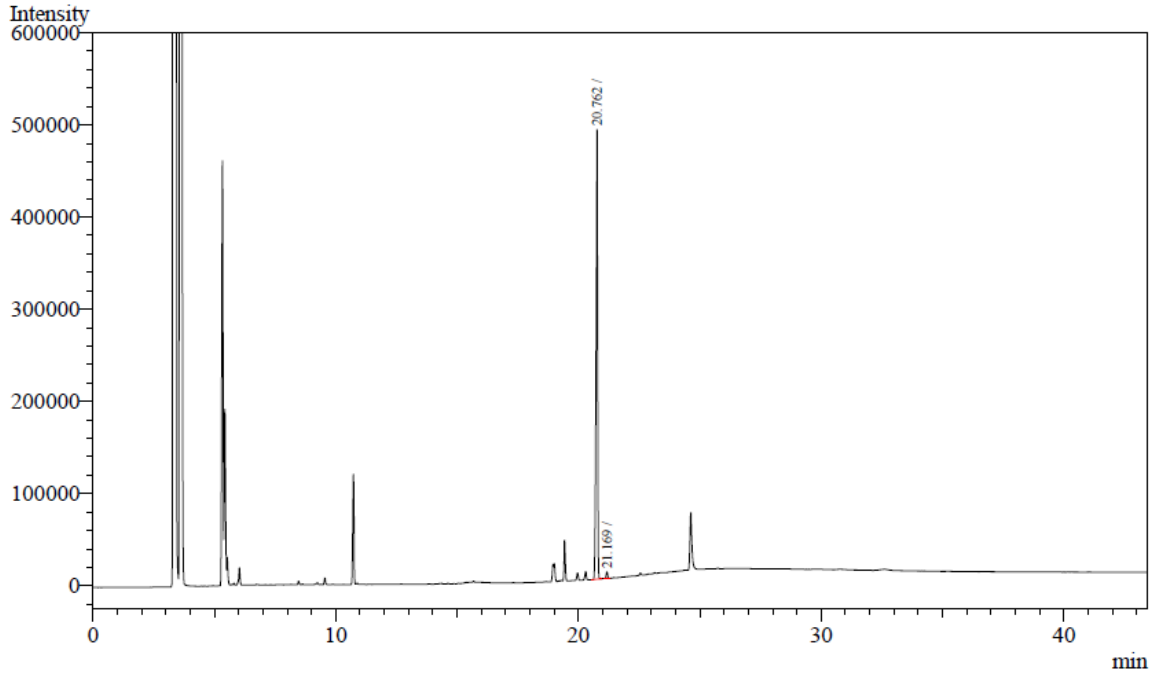
1-(2-isopropyl-5-methylcyclohexyl)-4-methoxybenzene 3-21k

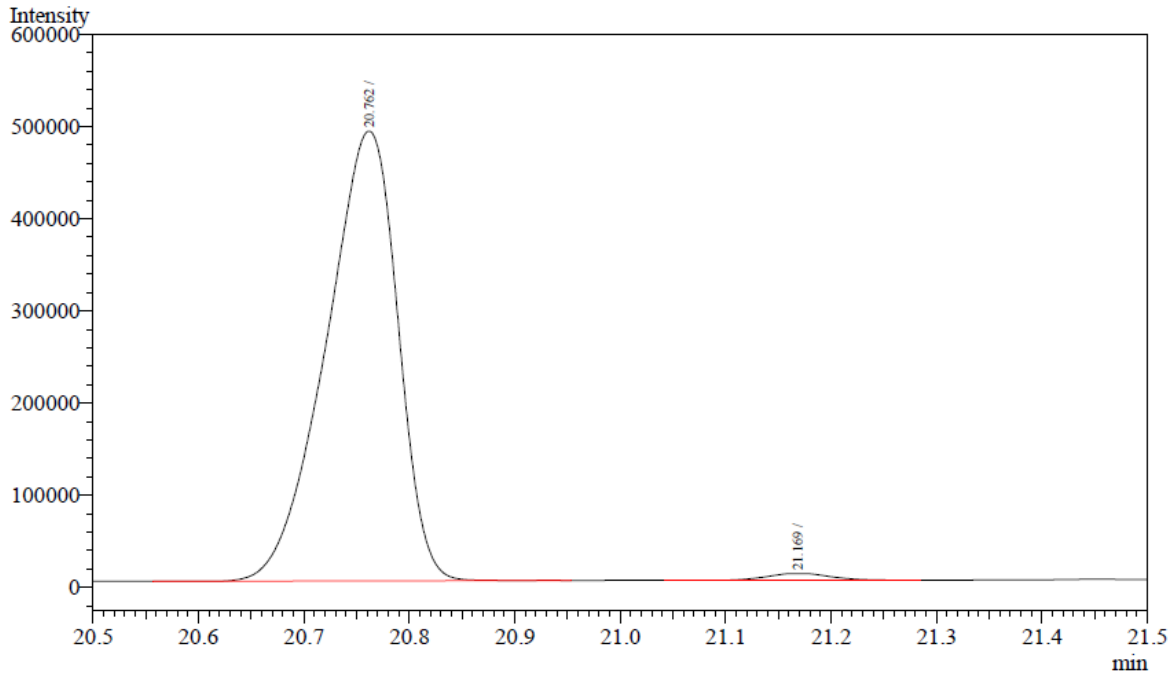


Chemical Formula: $C_{17}H_{26}O$
Exact Mass: 246.1984

Obtained as the mixture of cross-coupling products (143 mg colourless oil, 58% yield, 99:1selectivity, >99:1 d.r.) according to the **general procedure F with a modified conditions** (using 2.0 equiv alkyl bromide/Mg/LiCl,$ZnCl_2$, at 40 °C).

GC trace of the crude mixture with L^{13} as the ligand





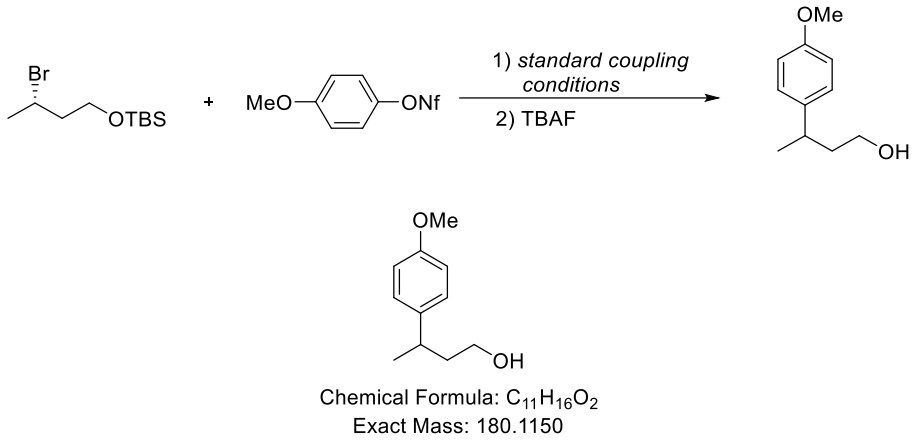
Peak#	Ret.Time	Area	Height	Conc.	Area%
1	20.762	2305169	487206	98.801	98.8013
2	21.169	27968	7185	1.199	1.1987
Total		2333137	494391	100.000	100.0000

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.12 – 7.04 (m, 2H), 6.87 – 6.78 (m, 2H), 3.79 (s, 3H), 2.38 (td, *J* = 11.6, 3.5 Hz, 1H), 1.85 – 1.70 (m, 3H), 1.51 – 1.36 (m, 3H), 1.19 – 0.97 (m, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.67 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 139.0, 128.4, 113.8, 55.3, 47.8, 47.2, 45.8, 35.5, 33.4, 27.5, 24.8, 22.7, 21.7, 15.5.

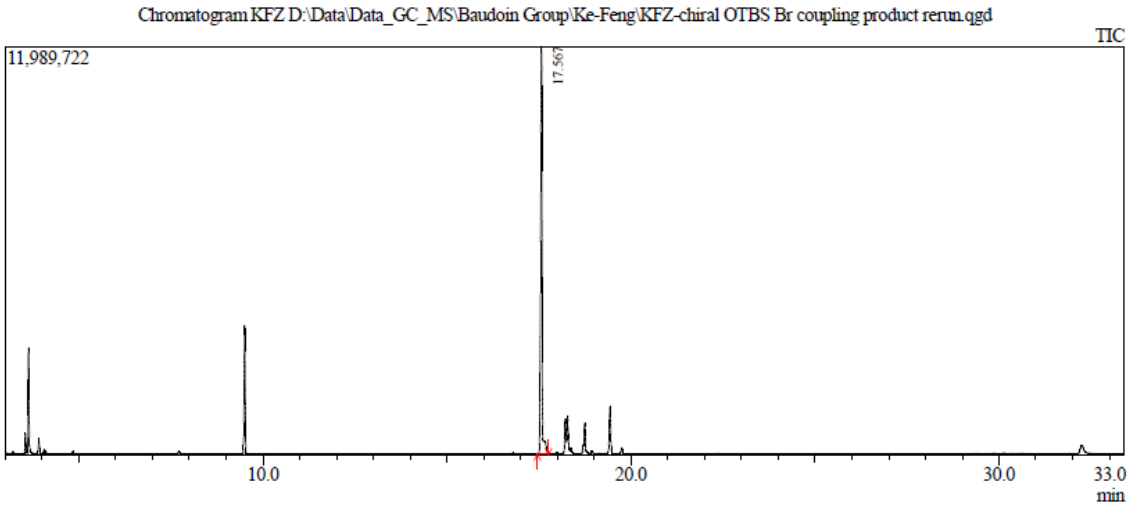
The NMR data for this compound was consistent with literature data.[155]

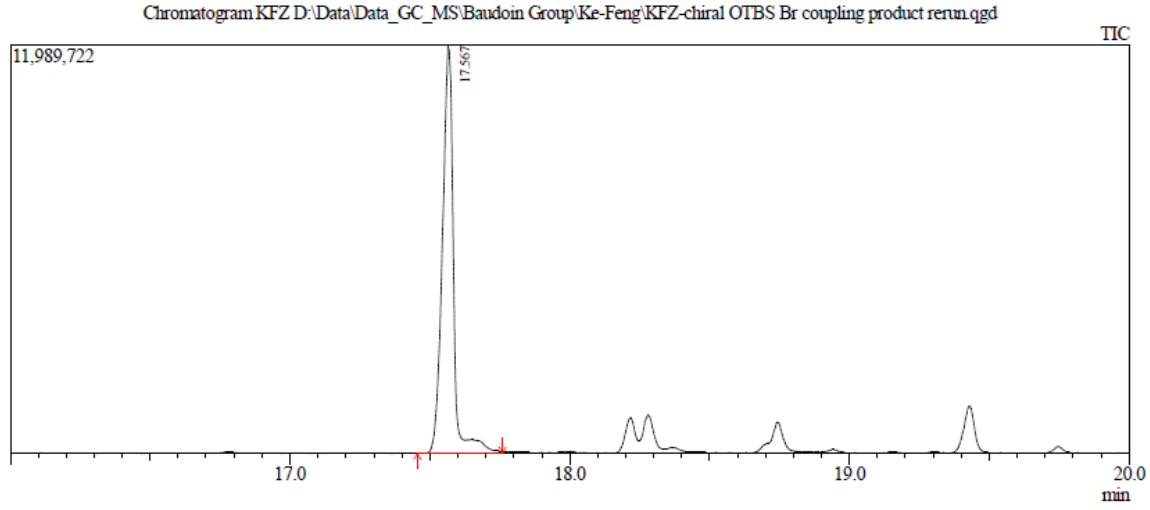
3-(4-methoxyphenyl)butan-1-ol 3-22



Obtained as pale yellow oil (90 mg, 50% yield, >99:1selectivity, ee: 3%.) according to the **general procedure F** and deprotection by TBAF.

GC-MS trace of the crude mixture (cross-coupling step) with L^{13} as the ligand





Peak Report TIC

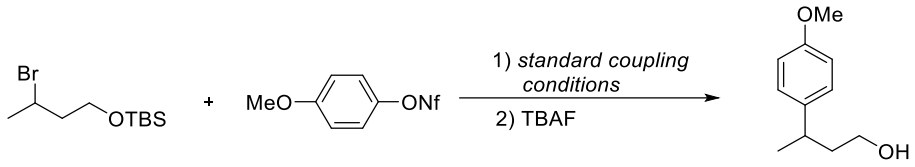
Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	17.567	17.455	17.760	33091921	100.00	11970198	100.00	2.76	MI	
				33091921	100.00	11970198	100.00			

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.10 (m, 2H), 6.88 – 6.81 (m, 2H), 3.79 (s, 3H), 3.63 – 3.47 (m, 2H), 2.83 (dt, *J* = 13.7, 6.9 Hz, 1H), 1.91 – 1.76 (m, 2H), 1.25 (d, *J* = 7.0 Hz, 3H), 1.20 (brs, 1H).

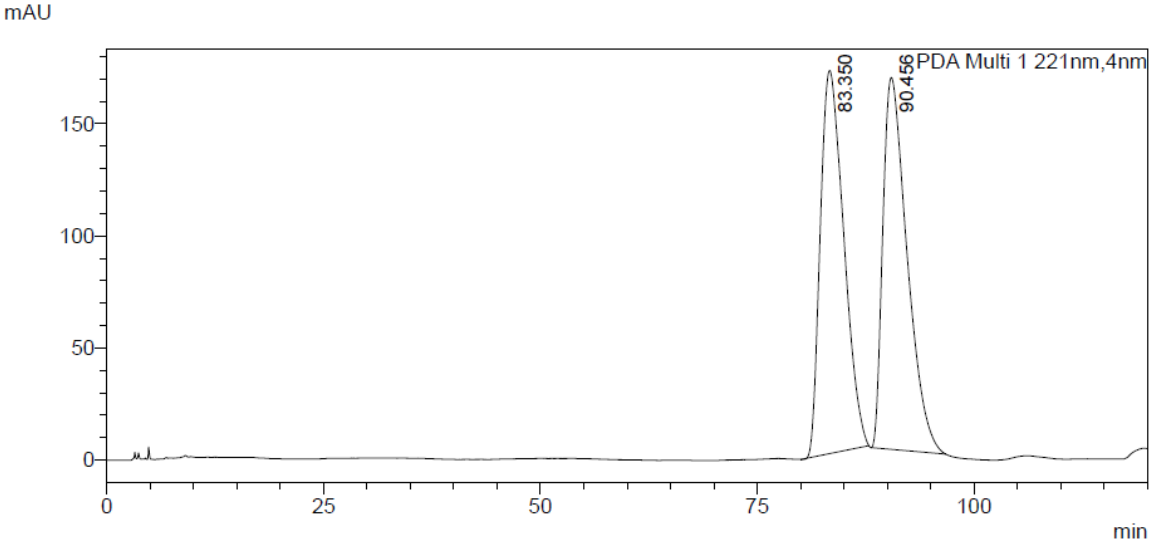
^{13}C NMR (126 MHz, Chloroform-*d*) δ 158.0, 139.0, 127.9, 114.0, 61.4, 55.4, 41.3, 35.8, 22.8.

HPLC conditions: DAICEL CHIRACEL OD-H, heptane/2-propanol = 99.5:0.5, flow rate = 1.0 mL/min, 25 °C, λ = 221 nm.

The NMR data for this compound was consistent with literature data.[156]



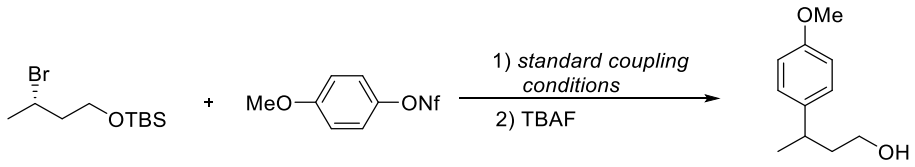
<Chromatogram>



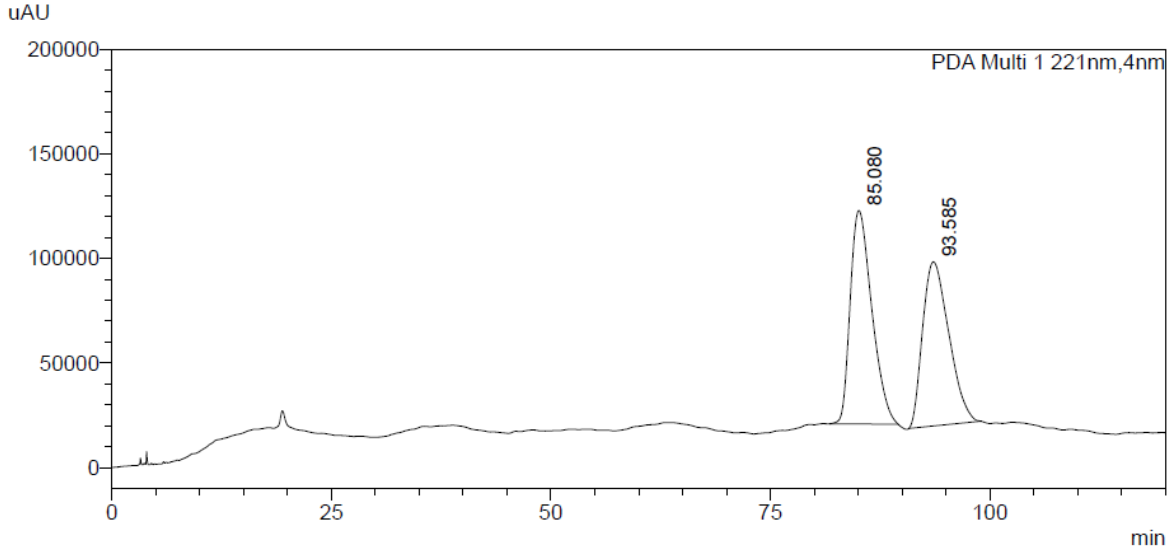
<Peak Table>

PDA Ch1 221nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	83.350	49.932	32119208	170853	0.000		M
2	90.456	50.068	32206586	165858	0.000		M
Total		100.000	64325794	336711			



<Chromatogram>



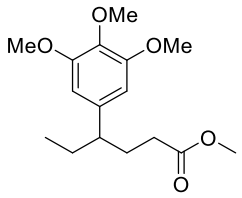
<Peak Table>

PDA Ch1 221nm

Peak#	Ret. Time	Area%	Area	Height	Conc.	Unit	Mark
1	85.080	51.764	17512259	102116	0.000		M
2	93.585	48.236	16318940	78552	0.000		M
Total		100.000	33831199	180668			

Procedure for scale-up reaction

methyl 4-(3,4,5-trimethoxyphenyl)hexanoate 3-21l

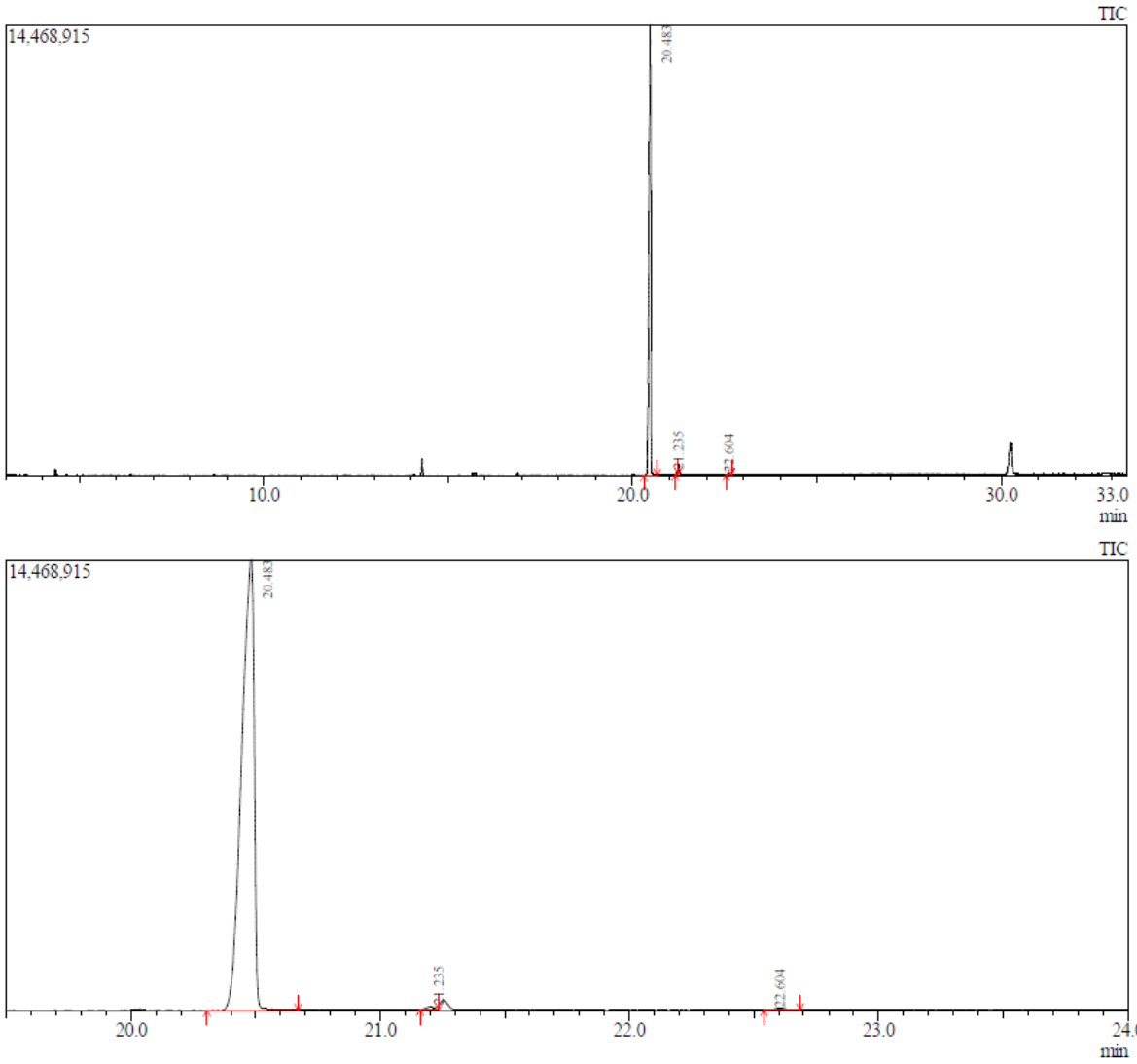


Chemical Formula: $C_{16}H_{24}O_5$
Exact Mass: 296.1624

An oven-dried 100 mL schlenk tube equipped with a stirring bar was taken into the glovebox, corresponding nonaflate (solid, 4.66 g, 10 mmol), magnesium powder (365 mg, 15 mmol), lithium chloride (636 mg, 15 mmol), zinc chloride (2.04 g, 15 mmol), Pd_2dba_3 (97%) (118 mg, 1.25 mol%) and **L**[13] (121 mg, 2.5 mol%) were added to the schlenk tube. The tube was capped with a septum and paraffin, and removed from the glovebox. Then, a solution of alkyl bromides (3.14 g, 15 mmol) in THF (25 mL) was added to the mixture via syringe under argon atmosphere. The septum was wrapped with paraffin and placed into a 25 °C water bath. The reaction mixture was stirred at that temperature for 48 h under argon. After that time, the reaction mixture was diluted with Et_2O (50 mL) and carefully quenched with saturated NH_4Cl

solution (30 mL) (An aliquot of the crude mixture was measured by GC-MS to determine the ratio of direct coupling product and migrative coupling product). The organic phase was separated and the aqueous phase was extracted with Et_2O (3 X 50 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography gave the desired product (2.2 g, 75%, >99:1) as a pale yellow oil.

GC-MS trace of the crude mixture with L^{13} as the ligand



Peak Report TIC

Peak#	R.Time	I.Time	F.Time	Area	Area%	Height	Height%	A/H	Mark	Name
1	20.483	20.305	20.670	50850218	99.11	14448101	98.61	3.52	MI	
2	21.235	21.160	21.235	306576	0.60	144688	0.99	2.12	MI	
3	22.604	22.540	22.685	149745	0.29	58462	0.40	2.56	MI	
				51306539	100.00	14651251	100.00			

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.32 (s, 2H), 3.84 (s, 6H), 3.82 (s, 3H), 3.62 (s, 3H), 2.38 – 2.28 (m, 1H), 2.19 – 2.12 (m, 2H), 2.05 – 1.95 (m, 1H), 1.83 – 1.74 (m, 1H), 1.63 – 1.49 (m, 2H), 0.80 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 174.3, 153.2, 140.4, 136.4, 104.6, 61.0, 56.2, 51.6, 47.9, 32.4, 31.6, 29.7, 12.3.

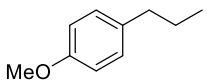
IR (neat): ν (cm^{-1}) 2957, 1736, 1589, 1509, 1322, 1238, 1128, 1011, 830, 772, 664.

HRMS (ESI): Calcd for $C_{16}H_{24}NaO_5$ $[M+Na]^+$: 319.1516, found: 319.1519.

General procedure G for Barbier-Negishi couplings of primary alkyl bromides

An oven-dried 10.0 – 20.0 mL Biotage microwave vial equipped with a stirring bar was taken into the glovebox, magnesium powder (2.0 e.q.), lithium chloride (2.0 e.q.), zinc chloride (2.0 e.q.), Pd_2dba_3 (97%) (5.0 mol%) and **L^{21}** (10.0 mol%) were added to the vial. The vial was capped with a Biotage cap using a crimper and removed from the glovebox. Then, a solution of sulfonates (1.0 mmol, 1.0 e.q.) and alkyl bromides (2.0 e.q.) in THF (5.0 mL, 0.2 M) was added to the mixture via syringe under argon atmosphere. The vial was wrapped with tape and placed into a 25 ^{o}C water bath. The reaction mixture was stirred at that temperature for 24 h. After that time, the reaction mixture was diluted with Et_2O (5.0 mL) and carefully quenched with saturated NH_4Cl solution (5.0 mL). The organic phase was separated and the aqueous phase was extracted with Et_2O (2 X 5.0 mL). The combined organic phases were dried over Na_2SO_4 and the solvent was removed *in vacuo*. Purification of the residue by silica gel column chromatography gave the desired product.

1-methoxy-4-propylbenzene 3-24b



Chemical Formula: $C_{10}H_{14}O$
Exact Mass: 150.1045

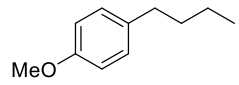
Obtained as a colourless oil (139 mg, 93% yield) according to the **general procedure G**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.05 (m, 2H), 6.90 – 6.76 (m, 2H), 3.80 (s, 3H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.70 – 1.54 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8, 134.9, 129.4, 113.8, 55.4, 37.3, 24.9, 13.9.

The NMR data for this compound was consistent with literature data.[73]

1-butyl-4-methoxybenzene 3-24c



Chemical Formula: $C_{11}H_{16}O$
Exact Mass: 164.1201

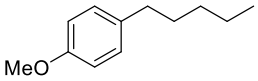
Obtained as a colourless oil (156 mg, 95% yield) according to the **general procedure G**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.06 (m, 2H), 6.88 – 6.79 (m, 2H), 3.80 (s, 3H), 2.60 – 2.53 (m, 2H), 1.63 – 1.53 (m, 2H), 1.42 – 1.32 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 135.2, 129.4, 113.8, 55.4, 34.9, 34.1, 22.5, 14.1.

The NMR data for this compound was consistent with literature data.[157]

1-methoxy-4-pentylbenzene 3-24a



Chemical Formula: $C_{12}H_{18}O$
Exact Mass: 178.1358

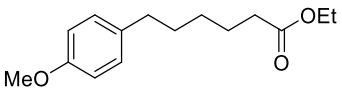
Obtained as a colourless oil (160 mg, 90% yield) according to the **general procedure G**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.16 – 7.04 (m, 2H), 6.89 – 6.77 (m, 2H), 3.80 (s, 3H), 2.56 (t, *J* = 7.7 Hz, 2H), 1.60 (dt, *J* = 15.2, 7.6 Hz, 2H), 1.40 – 1.28 (m, 4H), 0.91 (t, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 157.7, 135.2, 129.4, 113.8, 55.4, 35.2, 31.6, 31.6, 22.7, 14.2.

The NMR data for this compound was consistent with literature data.[73]

ethyl 6-(4-methoxyphenyl)hexanoate 3-24d



Chemical Formula: $C_{15}H_{22}O_3$
Exact Mass: 250.1569

Obtained as a pale yellow oil (235 mg, 94% yield) according to the **general procedure G**.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.14 – 7.04 (m, 2H), 6.88 – 6.75 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.62 – 2.48 (m, 2H), 2.29 (t, *J* = 7.6 Hz, 2H), 1.72 – 1.57 (m, 4H), 1.41 – 1.31 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H).

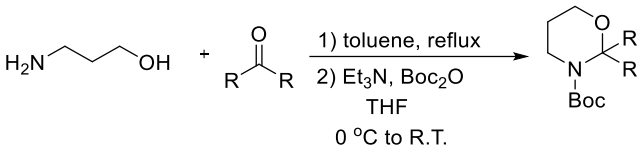
^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 157.8, 134.7, 129.3, 113.8, 60.3, 55.4, 34.9, 34.4, 31.4, 28.8, 25.0, 14.4.

The NMR data for this compound was consistent with literature data.[73]

4. Chapter 4: Enantioselective divergent arylation of *N*-Boc-tetrahydro-1,3-oxazine: Application to the synthesis of enantioenriched β^2- and β^3 -amino acids

General procedure

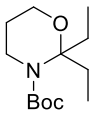
A: ***N-Boc-tetrahydro-1,3-oxazine synthesis***



To a solution of 3-aminopropan-1-ol (1.0 equiv.) in toluene (1.0 M) was added ketone (1.5 equiv.). The mixture was then stirred under reflux for 24 hours. After cooling to room temperature, the mixture was filtered and concentrated, and the residue was used directly for the next step.

To the solution of crude1,3-oxazinane (1.0 equiv.) and triethylamine (1.0 equiv.) in anhydrous THF (1.0 M), Boc_2O (1.0 equiv.) was added portionwise at 0 °C. The reaction was stirred for 10 min at 0 °C, warmed to room temperature and then stirred overnight. The mixture was diluted with water and extracted with ethyl acetate twice. The combined organic layers were dried over Na_2SO_4 and then concentrated under reduced pressure. The crude product was then purified by column chromatography on silica gel using Cyclohexane/Ethyl acetate as eluent to give the desired compound.

***tert*-butyl 2,2-diethyl-1,3-oxazinane-3-carboxylate 4-2b**



Chemical Formula: $C_{13}H_{25}NO_3$
Exact Mass: 243.1834

Obtained according to **General procedure A** as colourless oil (30% over two steps).

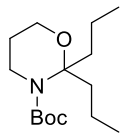
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.75 (t, *J* = 7.1 Hz, 2H), 3.62 – 3.49 (m, 2H), 2.09 (dq, *J* = 14.9, 7.5 Hz, 2H), 1.95 – 1.73 (m, 4H), 1.45 (s, 9H), 0.87 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 91.6, 79.7, 58.3, 39.3, 28.6, 24.3, 7.8. (one missing)

IR (neat): ν (cm^{-1}) 2971, 2881, 2361, 1688, 1390, 1168, 1091, 1026, 887, 769, 675, 628.

HRMS (ESI): Calcd for $C_{13}H_{25}NNaO_3$ $[M+Na]^+$: 266.1727, found: 266.1731.

***tert*-butyl 2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-2c**



Chemical Formula: $C_{15}H_{29}NO_3$
Exact Mass: 271.2147

Obtained according to **General procedure A** as white solid (25% over two steps).

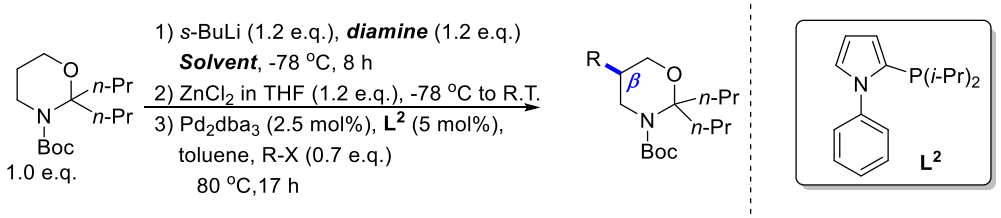
^{1}H NMR (400 MHz, Chloroform-*d*) δ 3.74 (t, *J* = 7.1 Hz, 2H), 3.58 – 3.48 (m, 2H), 2.04 (ddd, *J* = 14.1, 12.0, 4.6 Hz, 2H), 1.90 – 1.75 (m, 4H), 1.45 (s, 9H), 1.44 – 1.21 (m, 4H), 0.91 (t, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 91.2, 79.7, 58.4, 39.2, 38.7, 28.7, 24.3, 16.8, 14.5.

IR (neat): ν (cm^{-1}) 2956, 2875, 2361, 1683, 1365, 1282, 1162, 1088, 1016, 940, 891, 824, 777, 672.

HRMS (ESI): Calcd for $C_{15}H_{29}NNaO_3$ $[M+Na]^+$: 294.2040, found: 294.2038.

B: *β-Arylation of N-Boc-tetrahydro-1,3-oxazine derivatives*



B1: *Racemic version*

In a test-tube capped with rubber septum under argon, a solution of *N*-Boc-tetrahydro-1,3-oxazine (1.0 equiv., 0.5 mmol) and TMEDA (1.2 equiv.) in anhydrous THF (1.0 mL) was stirred and cooled to -78 °C (acetone/dry ice bath), and *s*-BuLi (1.6 M in hexane, 1.2 equiv.) was added slowly via syringe. The reaction was stirred for 5 h at this temperature before a solution of $ZnCl_2$ in THF (0.5 M, 1.2 equiv.) was added dropwise. The mixture was stirred for 30 min at -78 °C and then warmed to room temperature and

stirred for another 1 h. Solvents were removed *in vacuo*. Meanwhile, a solution of $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%) and **L²** (5.0 mol%) in toluene (1.5 mL) was prepared and stirred at room temperature for 15 min. The catalyst solution was added to the organozinc reagent tube followed by the addition of aryl bromides (0.7 equiv.). The reaction mixture was then allowed to stir at 80 °C for 17 h. After cooling to room temperature, saturated NH_4Cl solution (2.0 mL) was added and the mixture was extracted twice with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel yielding the desired product.

B2: ***Stoichiometric asymmetric version***

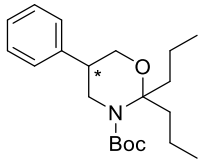
In a test-tube capped with rubber septum under argon, a solution of *N*-Boc-tetrahydro-1,3-oxazine (1.0 equiv., 0.5 mmol) and (+)-sparteine (1.2 equiv., (-)-sparteine was used in some cases) in anhydrous Et_2O (1.0 mL) was stirred and cooled to -78 °C (acetone/dry ice bath), and *s*-BuLi (1.6 M in hexane, 1.2 equiv.) was added slowly via syringe. The reaction was stirred for 8 h at this temperature before a solution of $ZnCl_2$ in THF (0.5 M, 1.2 equiv.) was added dropwise. The mixture was stirred for 30 min at -78 °C and then warmed to room temperature and stirred for another 1 h. Solvents were removed *in vacuo*. Meanwhile, a solution of $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%) and **L²** (5.0 mol%) in toluene (1.5 mL) was prepared and stirred at room temperature for 15 min. The catalyst solution was added to the organozinc reagent tube followed by the addition of aryl bromides (0.7 equiv.). The reaction mixture was then allowed to stir at 80 °C for 17 h. After cooling to room temperature, saturated NH_4Cl solution (2.0 mL) was added and the mixture was extracted twice with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel yielding the desired product.

B3: ***Catalytic asymmetric version***

In a test-tube capped with rubber septum under argon, *s*-BuLi (1.6 M in hexane, 1.2 equiv.) was added dropwise to a stirred solution of (+)-sparteine surrogate (0.3 equiv.) and di-*i*Pr-bispidine (1.3 equiv.) in anhydrous Et_2O (1.0 mL) at -78 °C. After stirring for 15 min at this temperature, a solution of *N*-Boc-tetrahydro-1,3-oxazine (1.0 equiv.) in anhydrous Et_2O (0.5 mL) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 8 h before a solution of $ZnCl_2$ in THF (0.5 M, 1.2 equiv.) was added dropwise. The reaction

mixture was stirred for 30 min at -78 °C and was then allowed to warm to room temperature and stirred for 1 hour. Solvents were removed *in vaccuo*. Meanwhile, a solution of $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%) and **L²** (5.0 mol%) was prepared in 1.5 mL of anhydrous toluene and allowed to stirred for 15 min at room temperature. The catalyst solution was added to the organozinc reagent tube followed by the addition of aryl bromide (0.7 equiv.). This mixture was conducted at 80 °C for 17 h. After cooling to room temperature, saturated NH_4Cl solution (2 mL) was added and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel yielding the desired product.

<u>*tert*-butyl 5-phenyl-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3ca</u>



Chemical Formula: $C_{21}H_{33}NO_3$
Exact Mass: 347.2460

Obtained as colourless oil (72% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.37 – 7.30 (m, 2H), 7.28 – 7.21 (m, 3H), 4.15 – 3.97 (m, 2H), 3.74 (dd, *J* = 11.7, 8.4 Hz, 1H), 3.32 (dd, *J* = 12.7, 11.1 Hz, 1H), 3.23 – 3.09 (m, 1H), 2.23 – 2.04 (m, 3H), 1.85– 1.70 (m, 1H), 1.56 – 1.47 (m, 2H), 1.46 (s, 9H), 1.40 – 1.26 (m, 2H), 0.94 (q, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 141.7, 128.8, 127.5, 127.1, 90.9, 79.9, 65.0, 45.8, 41.6, 39.2, 37.6, 28.6, 17.2, 16.5, 14.6, 14.5.

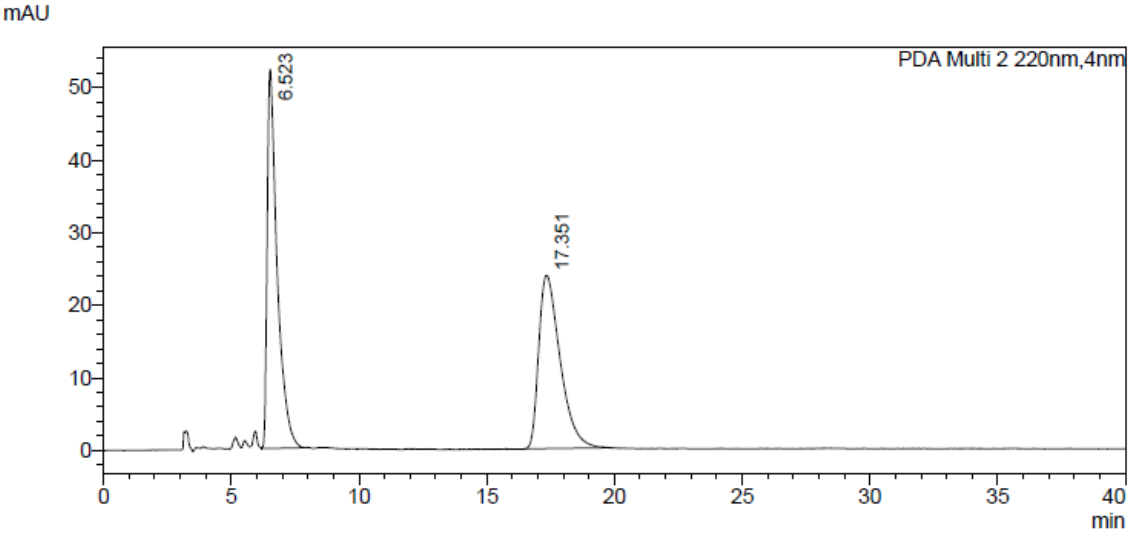
IR (neat): ν (cm^{-1}) 2961, 2362, 1688, 1455, 1365, 1246, 1163, 1107, 938, 831, 733, 660, 649.

HRMS (ESI): Calcd for $C_{21}H_{33}NNaO_3$ $[M+Na]^+$: 370.2353, found: 370.2354.

$[\alpha]_D^{20}$ = -22.4° (c = 0.56, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 220 nm, t_r(minor) = 7.1 min, t_r(major) = 16.8 min, 3.5:96.5 e.r.

<Chromatogram>



<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
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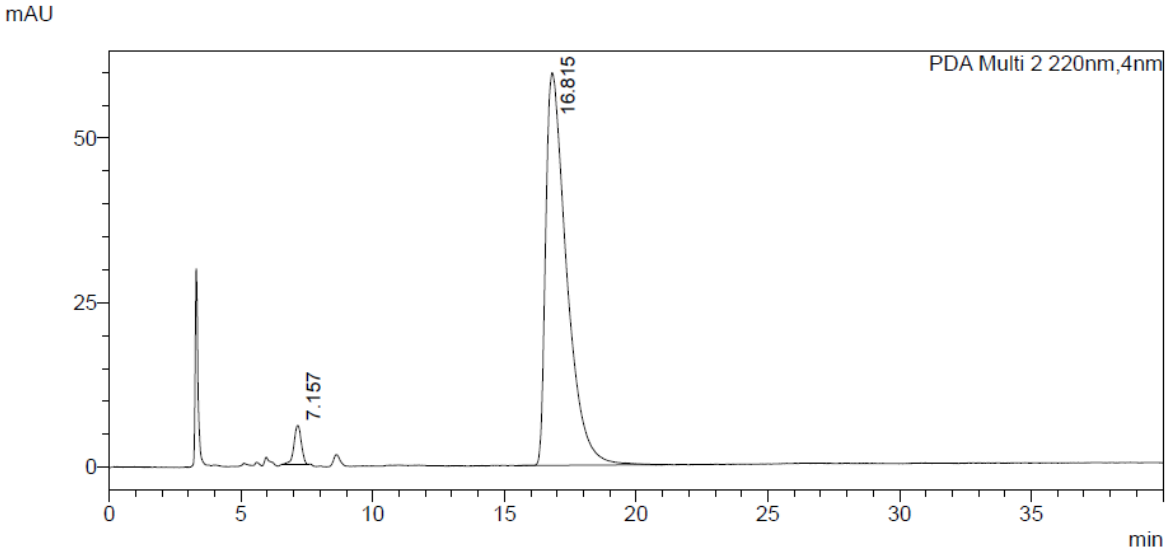
Total		2806568	76130	100.000

<Chromatogram>

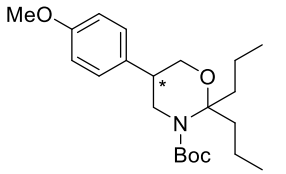


<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	7.157	114674	5923	3.374
2	16.815	3283981	59640	96.626
Total		3398655	65564	100.000

<u>*tert*-butyl 5-(4-methoxyphenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cb</u>



Chemical Formula: $C_{22}H_{35}NO_4$
Exact Mass: 377.2566

Obtained as colourless oil (72% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.20 – 7.11 (m, 2H), 6.90 – 6.81 (m, 2H), 4.08 – 3.96 (m, 2H), 3.79 (s, 3H), 3.69 (dd, *J* = 11.6, 8.5 Hz, 1H), 3.26 (dd, *J* = 12.7, 11.2 Hz, 1H), 3.16 – 3.03 (m, 1H), 2.20 – 2.04 (m, 3H), 1.82 – 1.70 (m, 1H), 1.55 – 1.47 (m, 2H), 1.45 (s, 9H), 1.39– 1.27 (m, 2H), 0.99 – 0.88 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 158.7, 154.1, 133.7, 128.4, 114.2, 90.8, 79.9, 65.2, 55.4, 46.0, 40.8, 39.3, 37.5, 28.6, 17.2, 16.5, 14.6, 14.5.

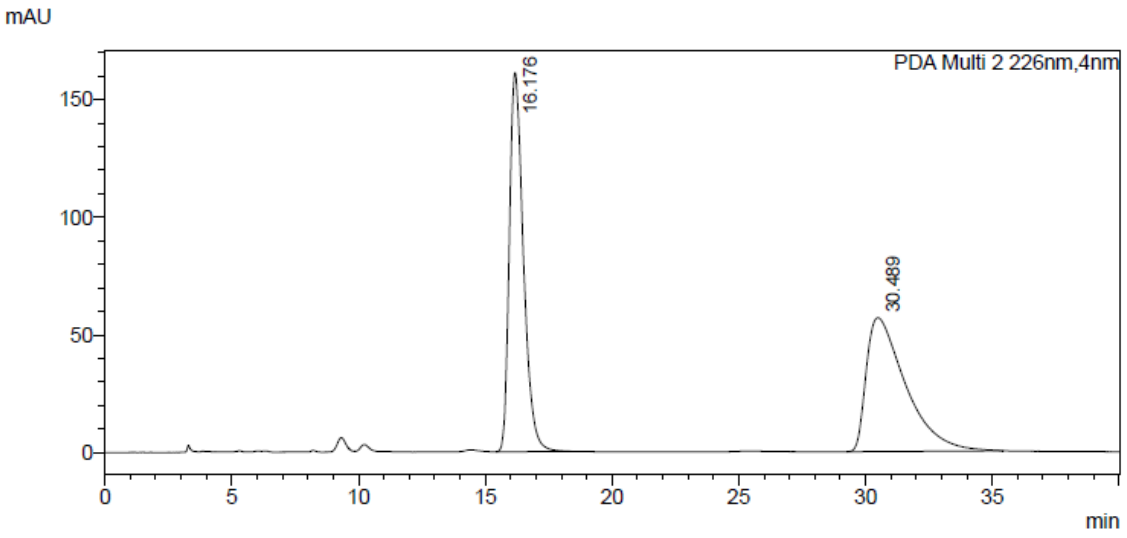
IR (neat): ν (cm^{-1}) 2960, 2361, 1688, 1613, 1514, 1458, 1391, 1247, 1171, 1103, 940, 826, 769, 631.

HRMS (ESI): Calcd for $C_{22}H_{35}NNaO_4$ $[M+Na]^+$: 400.2458, found: 400.2457.

$[\alpha]_D^{20}$ = -25.6° (c = 1.38, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 226 nm, t_r(minor) = 16.4 min, t_r(major) = 29.6 min, 3:97 e.r.

<Chromatogram>



<Peak Table>

PDA Ch2 226nm

Peak#	Ret. Time	Area	Height	Area%
1	16.176	6214109	161123	50.339
2	30.489	6130381	56844	49.661
Total		12344490	217968	100.000

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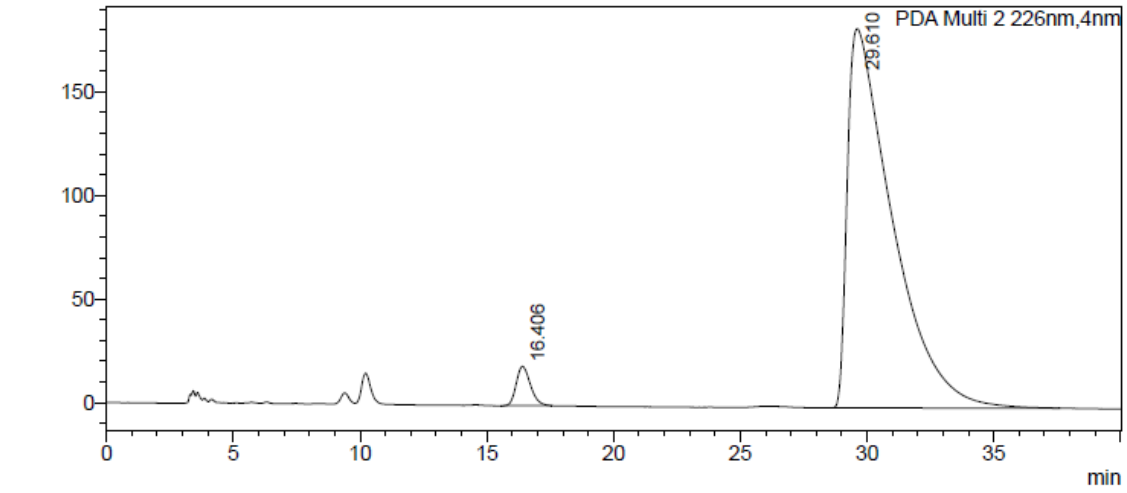
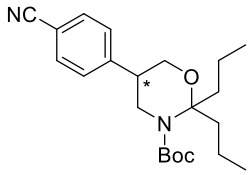


<Peak Table>

PDA Ch2 226nm

Peak#	Ret. Time	Area	Height	Area%
1	16.406	736501	19002	3.156
2	29.610	22600939	183160	96.844
Total		23337440	202162	100.000

<u>*tert*-butyl 5-(4-cyanophenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3ce</u>



Chemical Formula: $C_{22}H_{32}N_2O_3$
Exact Mass: 372.2413

Obtained as colourless oil (35% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.65 – 7.56 (m, 2H), 7.41 – 7.30 (m, 2H), 4.10 – 3.97 (m, 2H), 3.69 (dd, *J* = 11.9, 7.6 Hz, 1H), 3.37 (dd, *J* = 12.9, 10.1 Hz, 1H), 3.26 – 3.15 (m, 1H), 2.18 – 1.99 (m, 3H), 1.78 (ddd, *J* = 14.1, 12.0, 4.5 Hz, 1H), 1.51 – 1.47 (m, 1H), 1.45 (s, 9H), 1.41 – 1.22 (m, 3H), 0.92 (dt, *J* = 9.8, 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 147.4, 132.6, 128.3, 118.8, 111.1, 91.3, 80.3, 64.3, 45.1, 41.7, 38.8, 38.0, 28.6, 17.2, 16.5, 14.5, 14.4.

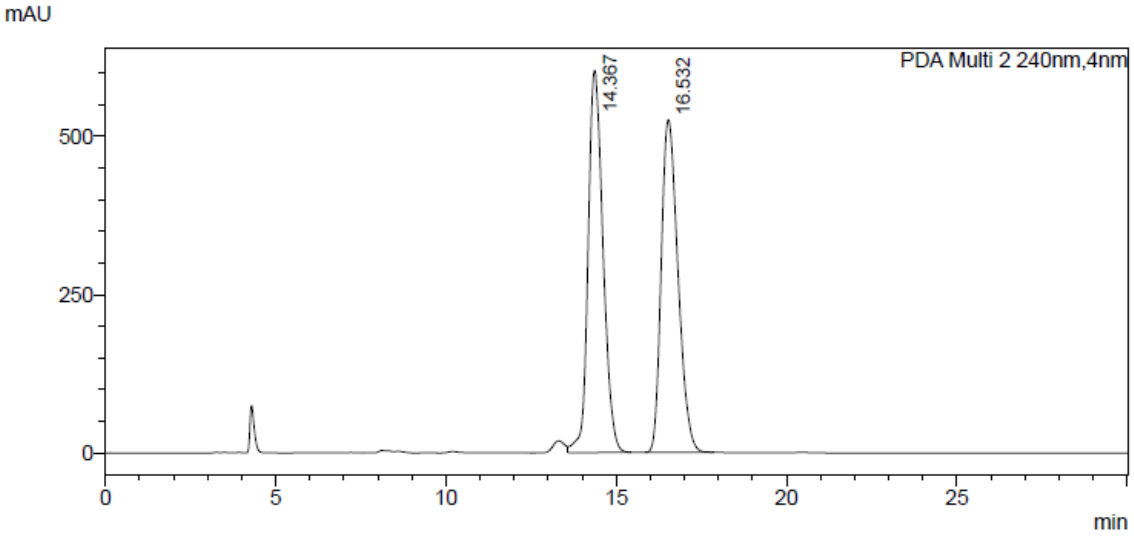
IR (neat): ν (cm^{-1}) 2961, 2361, 2229, 1686, 1609, 1457, 1392, 1282, 1246, 1163, 1103, 938, 826, 769.

HRMS (ESI): Calcd for $C_{22}H_{32}N_2NaO_3$ $[M+Na]^+$: 395.2305, found: 395.2307.

$[\alpha]_D^{20}$ = -28.9° (c = 1.1, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 240 nm, t_r(major) = 14.3 min, t_r(minor) = 16.5 min, 97:3 e.r.

<Chromatogram>

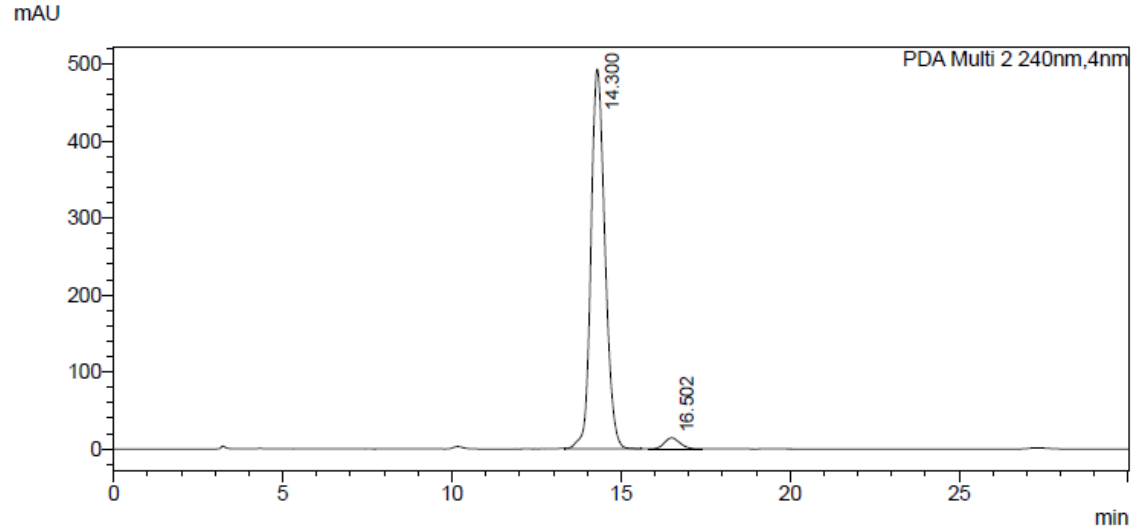


<Peak Table>

PDA Ch2 240nm

Peak#	Ret. Time	Area	Height	Area%
1	14.367	18411385	603999	50.615
2	16.532	17964216	526136	49.385
Total		36375602	1130134	100.000

<Chromatogram>

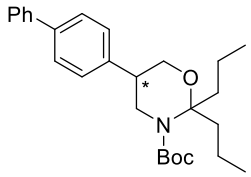


<Peak Table>

PDA Ch2 240nm

Peak#	Ret. Time	Area	Height	Area%
1	14.300	14247237	493358	96.961
2	16.502	446608	14266	3.039
Total		14693845	507624	100.000

tert-butyl 5-([1,1'-biphenyl]-4-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate



Chemical Formula: $C_{27}H_{37}NO_3$
Exact Mass: 423.2773

4-3ch, obtained as white solid (58% yield) according to **General procedure B2** using (+)-sparteine.

***ent*-4-3ch**, obtained as white solid (61% yield) according to **General procedure B2** using (-)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 – 7.52 (m, 4H), 7.47 – 7.40 (m, 2H), 7.37 – 7.30 (m, 3H), 4.17 – 4.02 (m, 2H), 3.77 (dd, *J* = 11.7, 8.3 Hz, 1H), 3.36 (dd, *J* = 12.7, 11.0 Hz, 1H), 3.28 – 3.12 (m, 1H), 2.23 – 2.06 (m, 3H), 1.79 (ddd, *J* = 14.0, 12.0, 4.5 Hz, 1H), 1.54 – 1.49 (m, 2H), 1.47 (s, 9H), 1.41 – 1.29 (m, 2H), 0.95 (q, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 140.9, 140.7, 140.1, 128.9, 127.9, 127.5, 127.4, 127.1, 91.0, 80.0, 65.0, 45.8, 41.3, 39.2, 37.6, 28.6, 17.2, 16.5, 14.6, 14.5.

IR (neat): ν (cm^{-1}) 2961, 1685, 1455, 1364, 1267, 1165, 1109, 938, 798, 699, 631.

HRMS (ESI): Calcd for $C_{27}H_{37}NNaO_3$ $[M+Na]^+$: 446.2666, found: 446.2664.

$[\alpha]_D^{20}$ = -21.8° (c = 1.35, $CHCl_3$) **(*from (+)-sparteine*)**

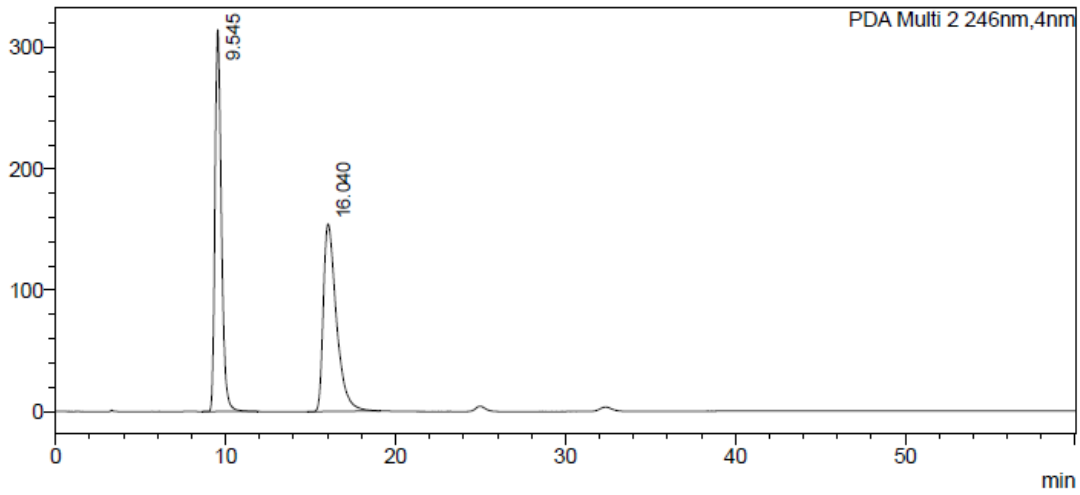
$[\alpha]_D^{20}$ = +46.7° (c = 0.69, $CHCl_3$) (***from (-)-sparteine***)

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 246 nm, t_r(minor) = 9.8 min, t_r(major) = 16.7 min, 3.5:96.5 e.r. **(*from (+)-sparteine*)**

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 246 nm, t_r(major) = 9.7 min, t_r(minor) = 16.8 min, 97:3 e.r. **(*from (-)-sparteine*)**

<Chromatogram>

mAU



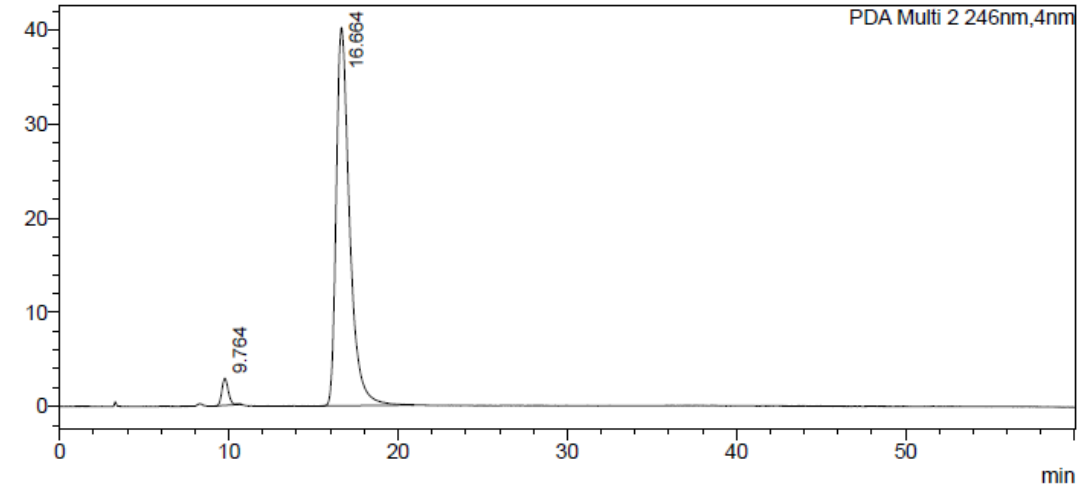
<Peak Table>

PDA Ch2 246nm

Peak#	Ret. Time	Area	Height	Area%
1	9.545	8303882	315032	50.055
2	16.040	8285684	154774	49.945
Total		16589566	469806	100.000

<Chromatogram>

mAU

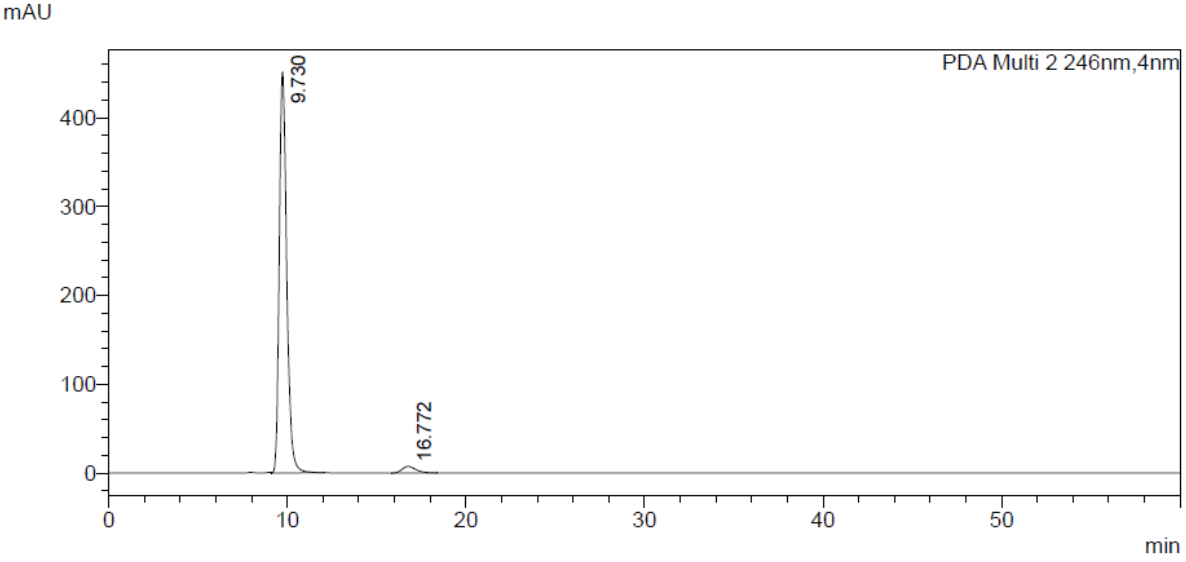


<Peak Table>

PDA Ch2 246nm

Peak#	Ret. Time	Area	Height	Area%
1	9.764	75509	2874	3.306
2	16.664	2208197	40195	96.694
Total		2283706	43069	100.000

<Chromatogram>

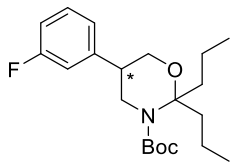


<Peak Table>

PDA Ch2 246nm

Peak#	Ret. Time	Area	Height	Area%
1	9.730	13091003	451366	97.036
2	16.772	399905	7406	2.964
Total		13490908	458772	100.000

***tert*-butyl 5-(3-fluorophenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3ci**



Chemical Formula: $C_{21}H_{32}FNO_3$
Exact Mass: 365.2366

Obtained as colourless oil (70% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 1H), 7.06 – 6.90 (m, 3H), 4.10 – 4.01 (m, 2H), 3.71 (dd, *J* = 11.8, 8.1 Hz, 1H), 3.34 (dd, *J* = 12.8, 10.7 Hz, 1H), 3.22 – 3.11 (m, 1H), 2.19 – 2.04 (m, 3H), 1.79 (ddd, *J* = 14.1, 11.9, 4.6 Hz, 1H), 1.57 – 1.50 (m, 1H), 1.47 (s, 9H), 1.45 – 1.26 (m, 3H), 0.95 (q, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.1 (d, *J* = 244.6 Hz), 154.1, 144.3 (d, *J* = 7.1 Hz), 130.2 (d, *J* = 8.2 Hz), 123.1 (d, *J* = 2.8 Hz), 114.3 (d, *J* = 21.3 Hz), 114.0 (d, *J* = 21.0 Hz), 91.0, 80.1, 64.7, 45.4, 41.3, 39.1, 37.7, 28.6, 17.2, 16.5, 14.5, 14.5.

^{19}F NMR (376 MHz, Chloroform-*d*) δ -112.7.

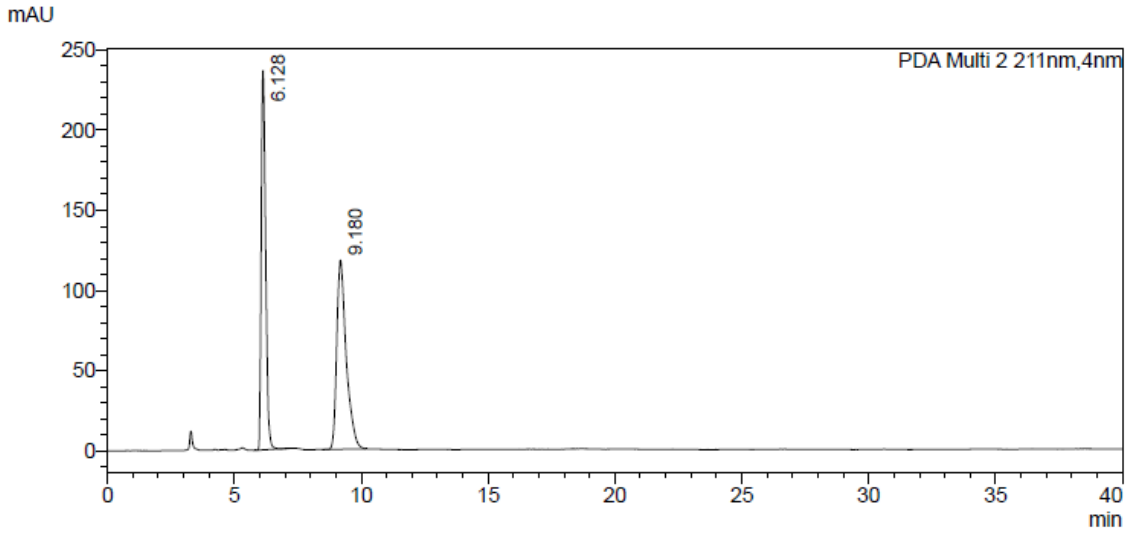
IR (neat): ν (cm^{-1}) 2961, 2361, 1688, 1590, 1452, 1366, 1245, 1160, 1108, 938, 783, 695, 629.

HRMS (ESI): Calcd for $C_{21}H_{32}FNNaO_3$ $[M+Na]^+$: 388.2258, found: 388.2257.

$[\alpha]_D^{20}$ = -16.9° (c = 1.23, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 211 nm, t_r(minor) = 6.1 min, t_r(major) = 9.0 min, 4:96 e.r.

<Chromatogram>

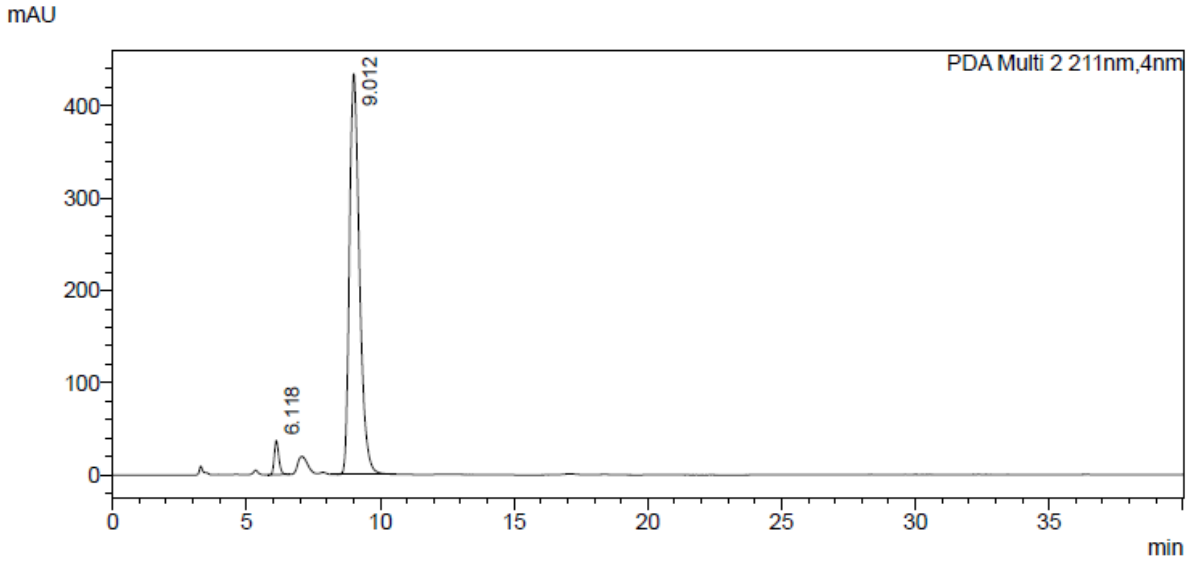


<Peak Table>

PDA Ch2 211nm

Peak#	Ret. Time	Area	Height	Area%
1	6.128	2859851	236477	48.236
2	9.180	3069037	117747	51.764
Total		5928888	354224	100.000

<Chromatogram>

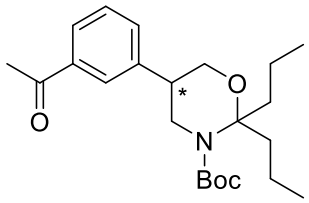


<Peak Table>

PDA Ch2 211nm

Peak#	Ret. Time	Area	Height	Area%
1	6.118	432800	36856	3.686
2	9.012	11307957	434157	96.314
Total		11740756	471013	100.000

***tert*-butyl 5-(3-acetylphenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cj**



Chemical Formula: $C_{23}H_{35}NO_4$
Exact Mass: 389.2566

Obtained as colourless oil (46% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.89–7.79 (m, 2H), 7.50 – 7.38 (m, 2H), 4.11 – 4.01 (m, 2H), 3.73 (dd, *J* = 11.8, 8.1 Hz, 1H), 3.39 (dd, *J* = 12.8, 10.6 Hz, 1H), 3.27 – 3.14 (m, 1H), 2.60 (s, 3H), 2.21 – 2.04 (m, 3H), 1.84 – 1.72 (m, 1H), 1.55 – 1.48 (m, 1H), 1.46 (s, 9H), 1.40 – 1.22 (m, 3H), 0.94 (q, *J* = 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 198.1, 154.1, 142.4, 137.6, 132.2, 129.1, 127.3, 127.2, 91.1, 80.1, 64.8, 45.5, 41.5, 39.1, 37.8, 28.6, 26.8, 17.2, 16.5, 14.6, 14.5.

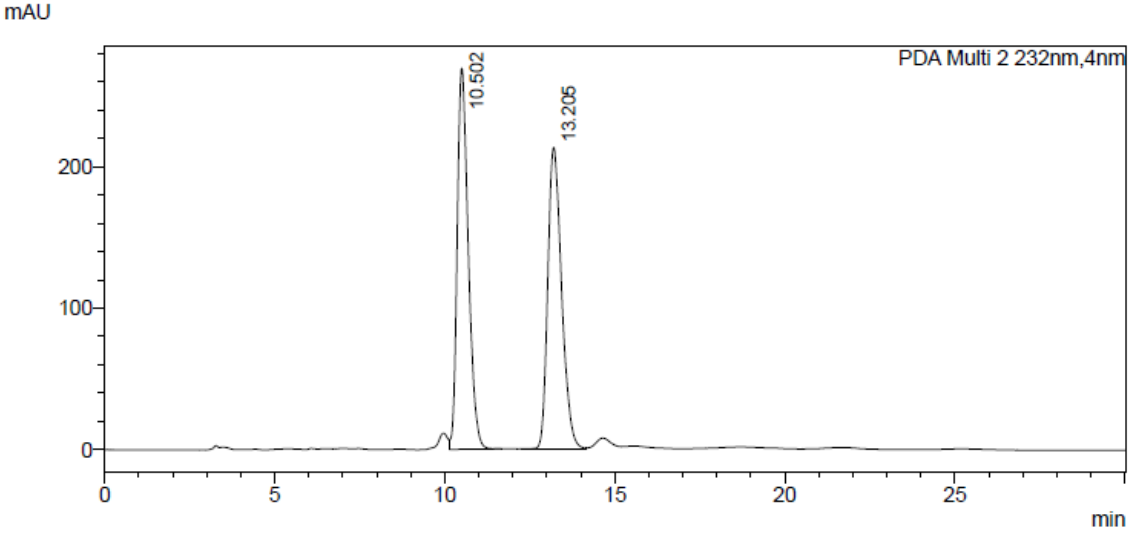
IR (neat): ν (cm^{-1}) 2961, 1685, 1455, 1364, 1267, 1165, 1109, 938, 699, 631.

HRMS (ESI): Calcd for $C_{23}H_{35}NNaO_4$ $[M+Na]^+$: 412.2458, found: 412.2464.

$[\alpha]_D^{20}$ = -22.0° (c = 0.91, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 232 nm, t_r(minor) = 10.6 min, t_r(major) = 13.3 min, 4:96 e.r.

<Chromatogram>

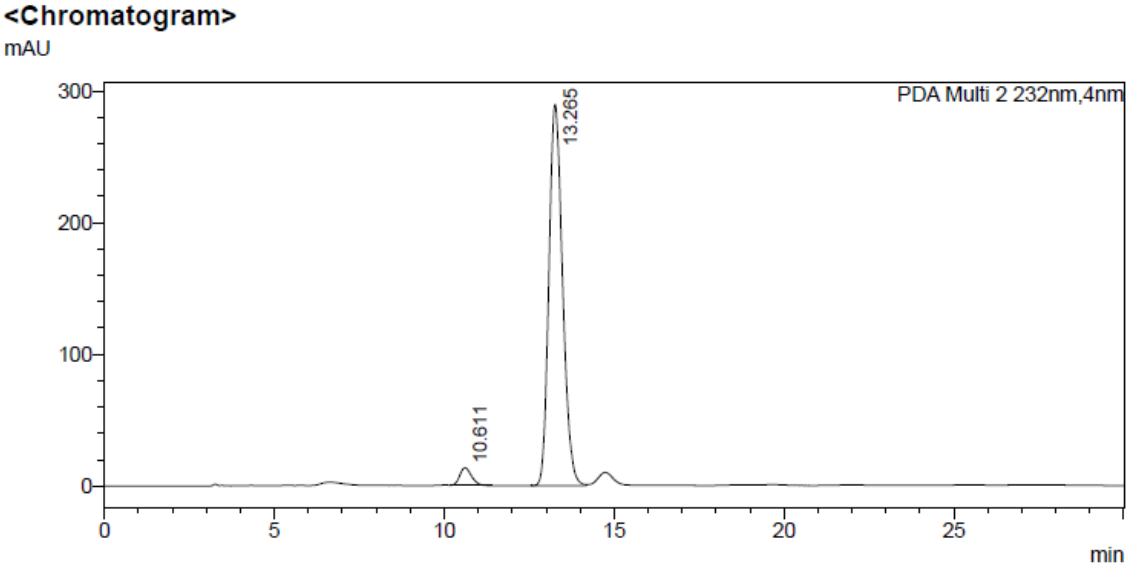


<Peak Table>

PDA Ch2 232nm

Peak#	Ret. Time	Area	Height	Area%
1	10.502	6091221	269284	50.307
2	13.205	6016836	212970	49.693
Total		12108058	482254	100.000

<Chromatogram>

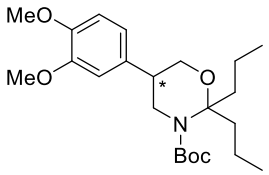


<Peak Table>

PDA Ch2 232nm

Peak#	Ret. Time	Area	Height	Area%
1	10.611	330486	13594	3.925
2	13.265	8089667	289417	96.075
Total		8420153	303011	100.000

***tert*-butyl 5-(3,4-dimethoxyphenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cm**



Chemical Formula: $C_{23}H_{37}NO_5$
Exact Mass: 407.2672

Obtained as colourless oil (68% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.84 – 6.72 (m, 3H), 4.08 – 3.97 (m, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.69 (dd, *J* = 11.7, 8.3 Hz, 1H), 3.30 (dd, *J* = 12.8, 10.9 Hz, 1H), 3.16 – 3.03 (m, 1H), 2.21 – 2.01 (m, 3H), 1.82 – 1.69 (m, 1H), 1.56 – 1.46 (m, 2H), 1.44 (s, 9H), 1.38 – 1.24 (m, 2H), 0.93 (q, *J* = 7.3 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 149.1, 148.1, 134.3, 119.3, 111.4, 110.7, 90.8, 79.9, 65.1, 56.0, 56.0, 45.8, 41.1, 39.2, 37.7, 28.6, 17.2, 16.5, 14.5, 14.5.

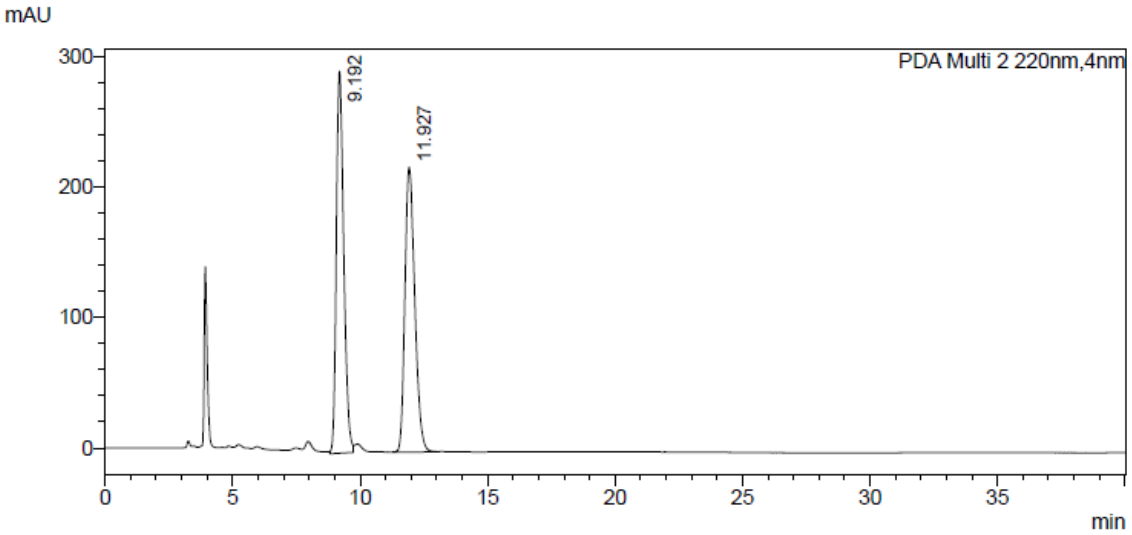
IR (neat): ν (cm^{-1}) 2960, 2361, 1686, 1518, 1459, 1391, 1251, 1159, 1107, 1029, 916, 806, 732, 646.

HRMS (ESI): Calcd for $C_{23}H_{37}NNaO_5$ $[M+Na]^+$: 430.2564, found: 430.2566.

$[\alpha]_D^{20}$ = -25.0° (c = 1.0, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 90:10, 1.0 mL/min, 220 nm, t_r(minor) = 9.1 min, t_r(major) = 11.8 min, 4:96 e.r.

<Chromatogram>

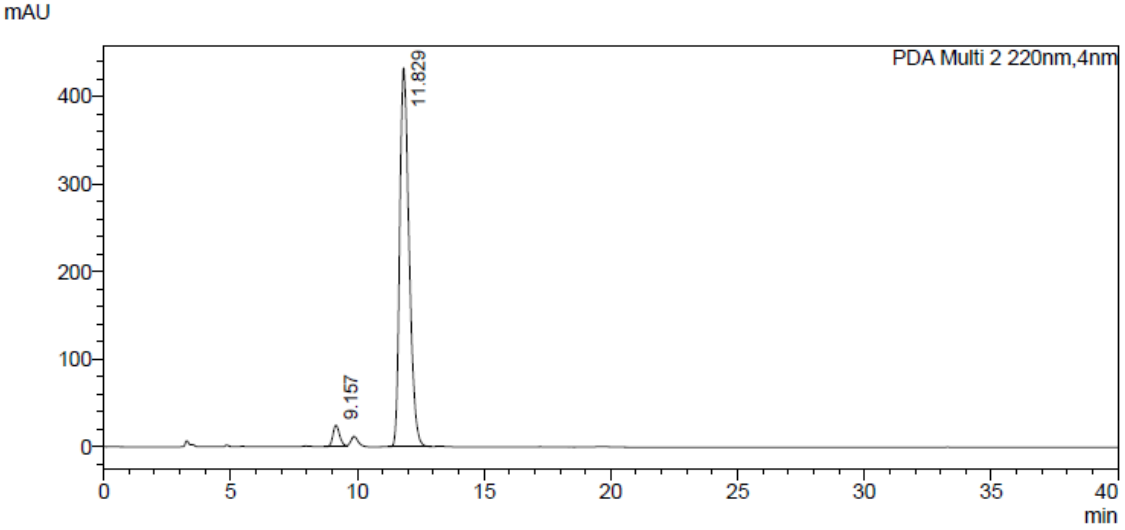


<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	9.192	5910135	292866	50.186
2	11.927	5866423	218358	49.814
Total		11776559	511224	100.000

<Chromatogram>

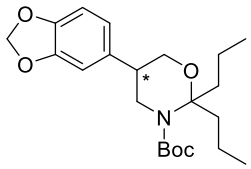


<Peak Table>

PDA Ch2 220nm

Peak#	Ret. Time	Area	Height	Area%
1	9.157	462637	24756	3.985
2	11.829	11146880	432839	96.015
Total		11609517	457595	100.000

***tert*-butyl 5-(benzo[d][1,3]dioxol-5-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate**



Chemical Formula: $C_{22}H_{33}NO_5$
Exact Mass: 391.2359

4-3cn, obtained as colourless oil (85% yield) according to **General procedure B2** using (+)-sparteine.

***ent*-4-3cn**, obtained as colourless oil (82% yield) according to **General procedure B2** using (-)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 6.76 – 6.72 (m, 2H), 6.70 – 6.65 (m, 1H), 5.92 (s, 2H), 4.10 – 3.91 (m, 2H), 3.65 (dd, *J* = 11.7, 8.3 Hz, 1H), 3.24 (dd, *J* = 12.7, 11.0 Hz, 1H), 3.12 – 3.01 (m, 1H), 2.19 – 2.02 (m, 3H), 1.81 – 1.70 (m, 1H), 1.53 – 1.47 (m, 1H), 1.45 (s, 9H), 1.44 – 1.23 (m, 3H), 0.93 (td, *J* = 7.4, 5.0 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 148.0, 146.6, 135.5, 120.5, 108.5, 107.7, 101.1, 90.9, 79.9, 65.1, 45.9, 41.3, 39.2, 37.6, 28.6, 17.2, 16.4, 14.6, 14.5.

IR (neat): ν (cm^{-1}) 2961, 2361, 1684, 1488, 1444, 1393, 1247, 1166, 1103, 1041, 910, 809, 731, 647.

HRMS (ESI): Calcd for $C_{22}H_{33}NNaO_5$ $[M+Na]^+$: 414.2251, found: 414.2253.

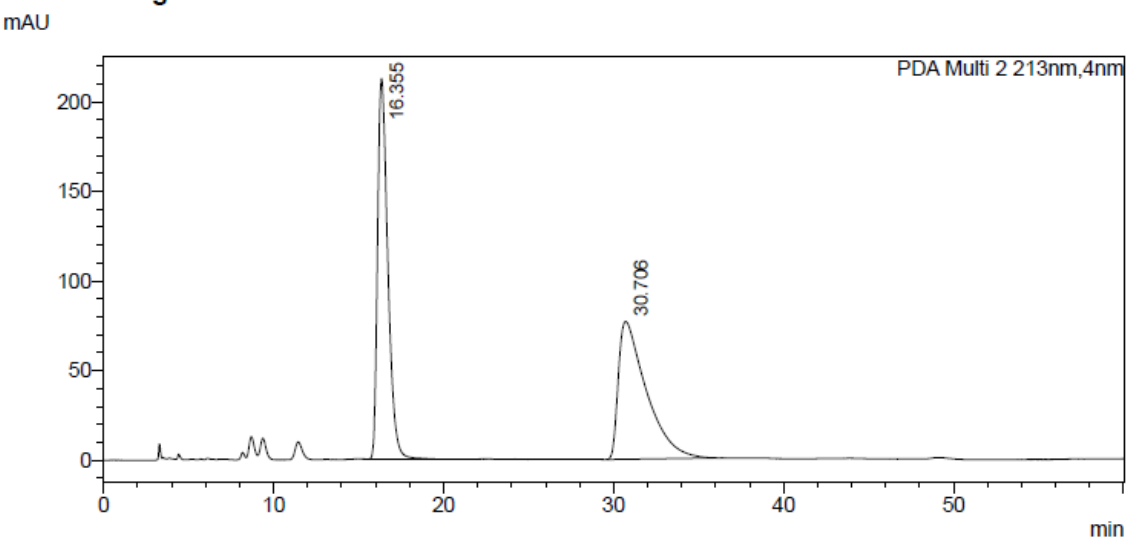
$[\alpha]_D^{20}$ = -27.6° (c = 1.35, $CHCl_3$) (***from (+)-sparteine***)

$[\alpha]_D^{20}$ = +25.6° (c = 0.59, $CHCl_3$) (***from (-)-sparteine***)

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 213 nm, t_r(minor) = 16.3 min, t_r(major) = 31.3 min, 4:96 e.r. (***from (+)-sparteine***)

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 213 nm, t_r(major) = 15.8 min, t_r(minor) = 32.5 min, 97:3 e.r. (***from (-)-sparteine***)

<Chromatogram>

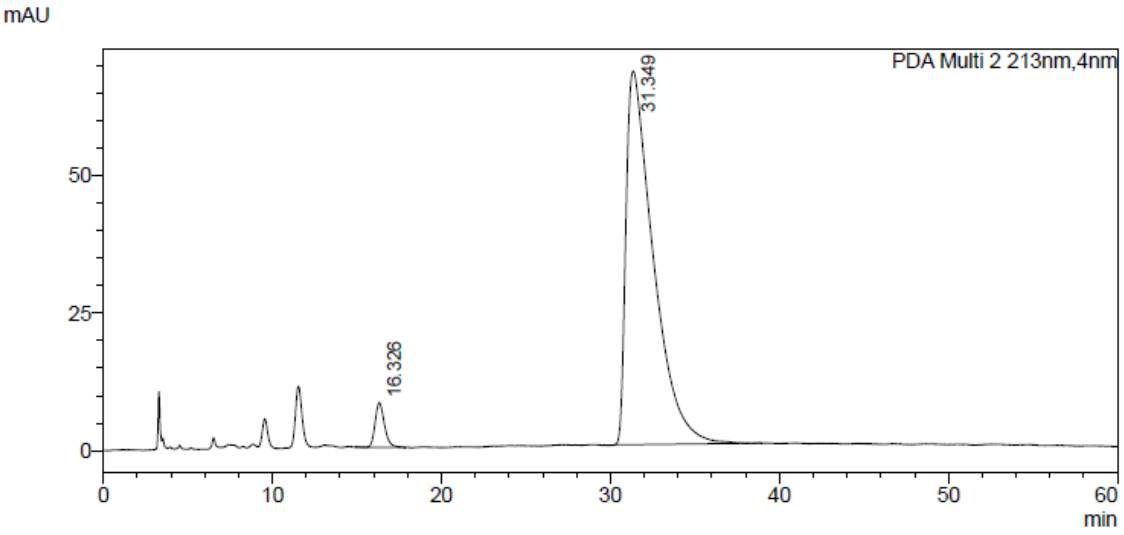


<Peak Table>

PDA Ch2 213nm

Peak#	Ret. Time	Area	Height	Area%
1	16.355	8934662	212326	50.444
2	30.706	8777520	76864	49.556
Total		17712181	289190	100.000

<Chromatogram>

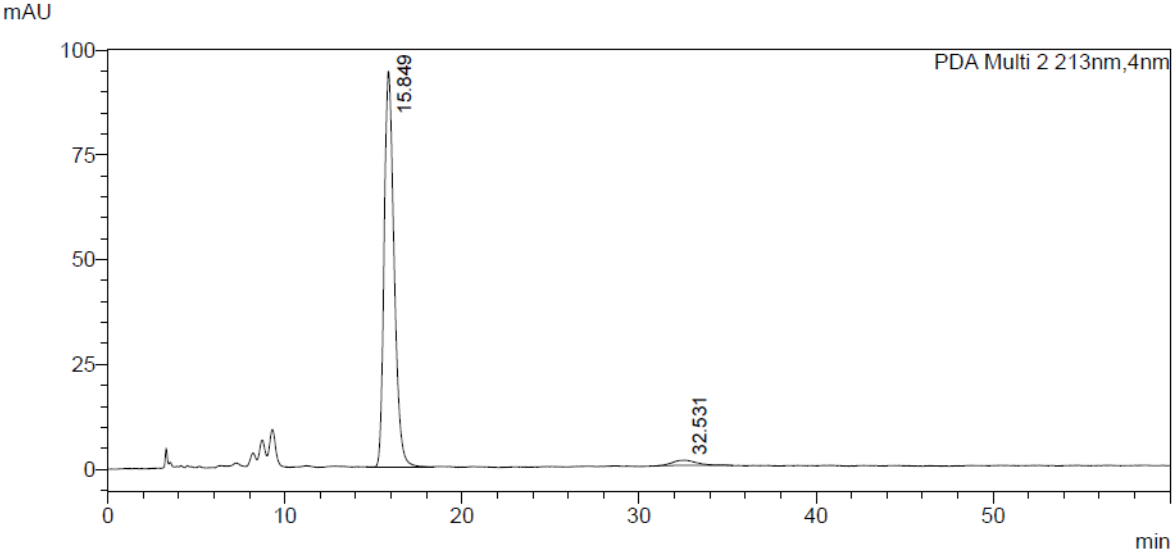


<Peak Table>

PDA Ch2 213nm

Peak#	Ret. Time	Area	Height	Area%
1	16.326	309841	8111	3.908
2	31.349	7619369	67863	96.092
Total		7929210	75974	100.000

<Chromatogram>

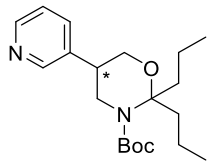


<Peak Table>

PDA Ch2 213nm

Peak#	Ret. Time	Area	Height	Area%
1	15.849	3694406	94464	96.911
2	32.531	117771	1266	3.089
Total		3812177	95729	100.000

***tert*-butyl 2,2-dipropyl-5-(pyridin-3-yl)-1,3-oxazinane-3-carboxylate 4-3cp**



Chemical Formula: $C_{20}H_{32}N_2O_3$
Exact Mass: 348.2413

Obtained as colourless oil (66% yield of mixture of *β*- and *γ*-products) according to **General procedure B2** using (+)-sparteine.

The data shown below is the characterization for the major *β*-product.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.54 – 8.44 (m, 2H), 7.60 – 7.54 (m, 1H), 7.28 – 7.21 (m, 1H), 4.08 – 3.99 (m, 2H), 3.69 (dd, *J* = 11.8, 7.8 Hz, 1H), 3.35 (dd, *J* = 12.9, 10.4 Hz, 1H), 3.21 – 3.11 (m, 1H), 2.10 – 1.99 (m, 3H), 1.81 – 1.72 (m, 1H), 1.64 – 1.48 (m, 1H), 1.43 (s, 9H), 1.38 – 1.22 (m, 3H), 0.98 – 0.83 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.0, 149.3, 148.6, 137.2, 134.7, 123.7, 91.1, 80.2, 64.4, 45.3, 40.7, 39.1, 37.8, 28.5, 17.1, 16.5, 14.5, 14.4.

IR (neat): ν (cm^{-1}) 2960, 2361, 1687, 1457, 1365, 1241, 1162, 1105, 939, 715, 666, 628.

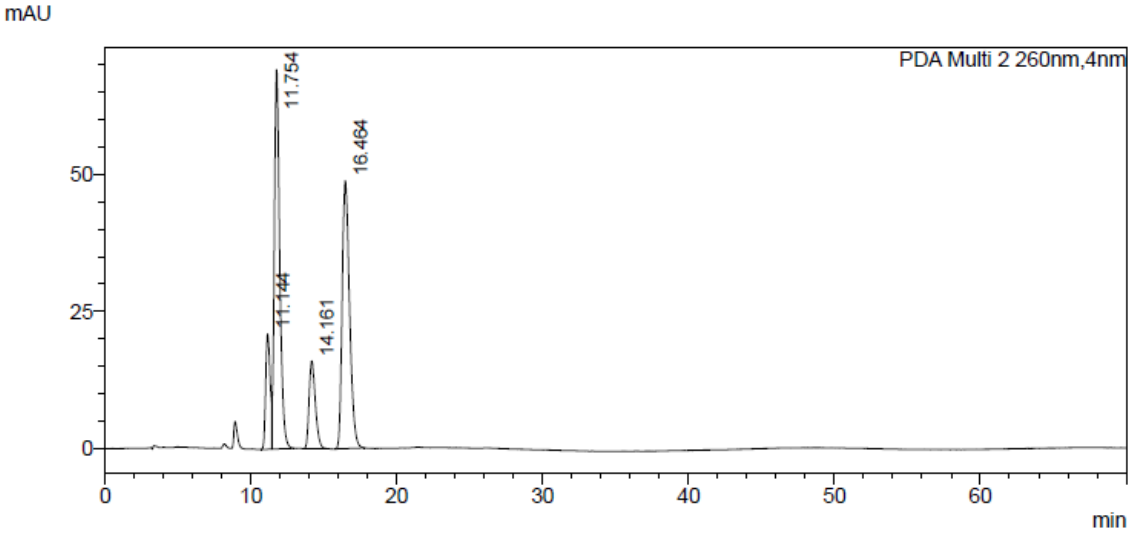
HRMS (ESI): Calcd for $C_{20}H_{33}N_2O_3$ $[M+H]^+$: 349.2486, found: 349.2486.

HPLC separation:

***β*-product (major)**: Chiralpak IC, *n*-Heptane/*i*-PrOH = 90:10, 1.0 mL/min, 260 nm, t_r(minor) = 11.8 min, t_r(major) = 16.4 min, 5:95 e.r.

***γ*-product (minor)**: Chiralpak IC, *n*-Heptane/*i*-PrOH = 90:10, 1.0 mL/min, 260 nm, t_r(minor) = 11.2 min, t_r(major) = 14.2 min, 4:96 e.r.

<Chromatogram>

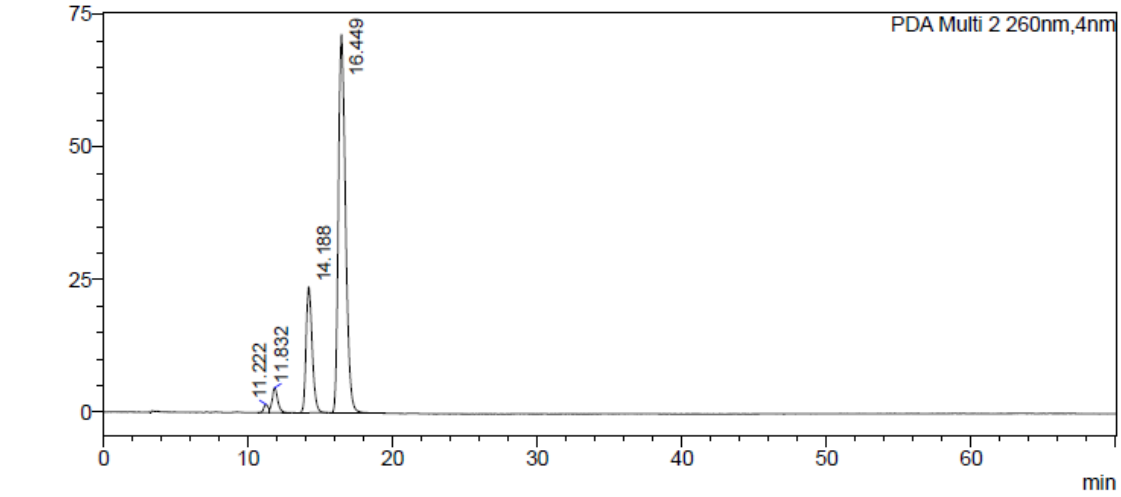


<Peak Table>

PDA Ch2 260nm

Peak#	Ret. Time	Area	Height	Area%
1	11.144	450739	21014	10.178
2	11.754	1785380	69144	40.315
3	14.161	477031	15969	10.772
4	16.464	1715424	48807	38.735
Total		4428575	154935	100.000

<Chromatogram>



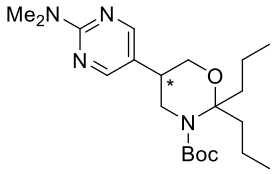
<Peak Table>

PDA Ch2 260nm

Peak#	Ret. Time	Area	Height	Area%
1	11.222	32590	1560	0.982
2	11.832	124367	4701	3.746
3	14.188	699994	23734	21.087
4	16.449	2462609	71375	74.185
Total		3319559	101370	100.000

<u>*tert*-butyl</u>

<u>5-(2-(dimethylamino)pyrimidin-5-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cq</u>



Chemical Formula: $C_{21}H_{36}N_4O_3$
Exact Mass: 392.278

Obtained as colourless oil (64% yield of mixture of *β*- and *γ*-products) according to **General procedure B2** using (+)-sparteine.

The data shown below is the characterization for the major *β*-product.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.21 – 8.16 (m, 2H), 3.99 – 3.91 (m, 2H), 3.59 (dd, *J* = 11.8, 8.3 Hz, 1H), 3.23 (dd, *J* = 12.9, 10.7 Hz, 1H), 3.14 (s, 6H), 3.00 – 2.87 (m, 1H), 2.06 – 1.91 (m, 3H), 1.76 – 1.69 (m, 1H), 1.53 – 1.46 (m, 1H), 1.42 (s, 9H), 1.34 – 1.21 (m, 3H), 0.94 – 0.86 (m, 6H).

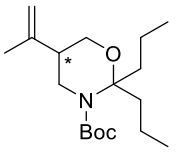
^{13}C NMR (101 MHz, Chloroform-*d*) δ 161.8, 156.7, 154.0, 121.2, 91.0, 80.1, 64.5, 45.5, 40.7, 39.1, 37.2, 37.2, 36.3, 28.5, 17.1, 16.4, 14.5, 14.4.

IR (neat): ν (cm^{-1}) 2960, 2361, 1689, 1605, 1537, 1388, 1161, 1106, 939, 658.

HRMS (ESI): Calcd for $C_{21}H_{37}N_4O_3$ $[M+H]^+$: 393.2860, found: 393.2864.

HPLC separation: did not find good conditions to separate it on chiral HPLC.

***tert*-butyl 5-(prop-1-en-2-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cs**



Chemical Formula: $C_{18}H_{33}NO_3$
Exact Mass: 311.2460

Obtained as colourless oil (82% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.80 – 4.77 (m, 1H), 4.75 – 4.71 (m, 1H), 3.98 – 3.78 (m, 2H), 3.50 (dd, *J* = 11.5, 8.6 Hz, 1H), 3.11 (dd, *J* = 12.7, 10.8 Hz, 1H), 2.62 – 2.49 (m, 1H), 2.13 – 1.94 (m, 3H), 1.72 (s, 3H), 1.70 – 1.64 (m, 1H), 1.45 (s, 9H), 1.41 – 1.19 (m, 4H), 0.93 – 0.87 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.1, 144.4, 111.4, 90.8, 79.8, 62.7, 43.5, 42.2, 39.2, 37.7, 28.6, 20.9, 17.2, 16.4, 14.5, 14.5.

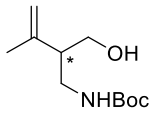
IR (neat): ν (cm^{-1}) 2962, 2361, 1684, 1456, 1377, 1166, 1110, 908, 733, 670, 629.

HRMS (ESI): Calcd for $C_{18}H_{33}NNaO_3$ $[M+Na]^+$: 334.2353, found: 334.2353.

$[\alpha]_D^{20}$ = -14.2° (c = 0.87, $CHCl_3$).

The e.r. was determined by the corresponding amino alcohol.

***tert*-butyl (2-(hydroxymethyl)-3-methylbut-3-en-1-yl)carbamate**



Chemical Formula: $C_{11}H_{21}NO_3$
Exact Mass: 215.1521

^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.93 (s, 1H), 4.75 (s, 1H), 4.71 (brs, 1H), 3.68 – 3.52 (m, 2H), 3.37 – 3.15 (m, 2H), 2.73 (brs, 1H), 2.38 – 2.22 (m, 1H), 1.74 (s, 3H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 157.0, 143.8, 113.0, 79.9, 61.8, 49.0, 39.8, 28.5, 21.7.

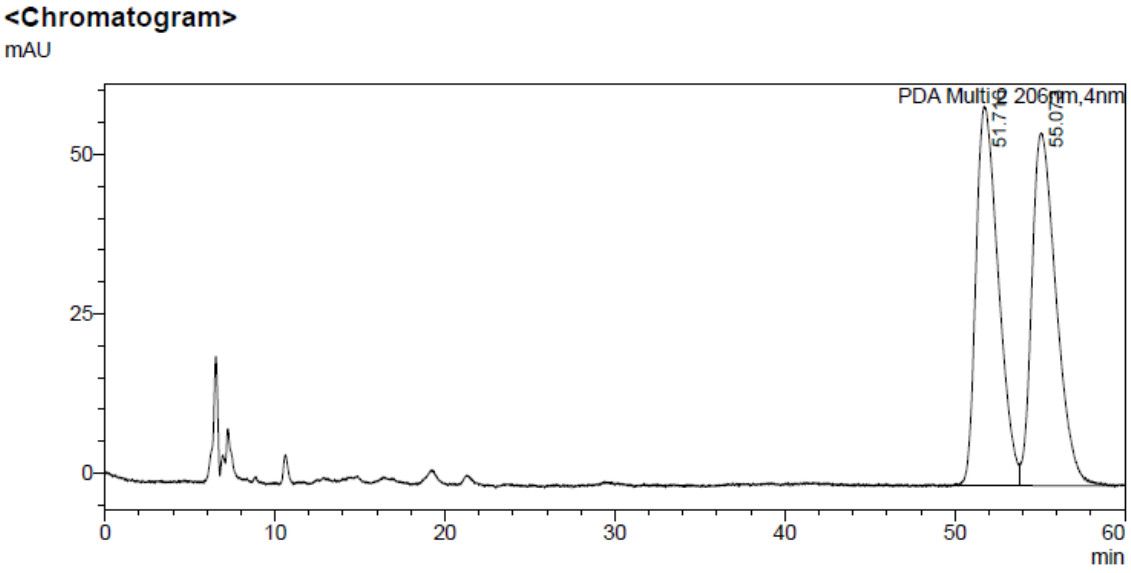
IR (neat): ν (cm^{-1}) 3355, 2976, 2361, 1687, 1511, 1366, 1250, 1167, 1039, 893, 670.

HRMS (ESI): Calcd for $C_{11}H_{21}NNaO_3$ $[M+Na]^+$: 238.1414, found: 238.1414.

$[\alpha]_D^{20}$ = +6.5° (c = 1.53, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 0.5 mL/min, 206 nm, t_r(minor) = 52.3 min, t_r(major) = 55.2 min, 4:96 e.r.

<Chromatogram>

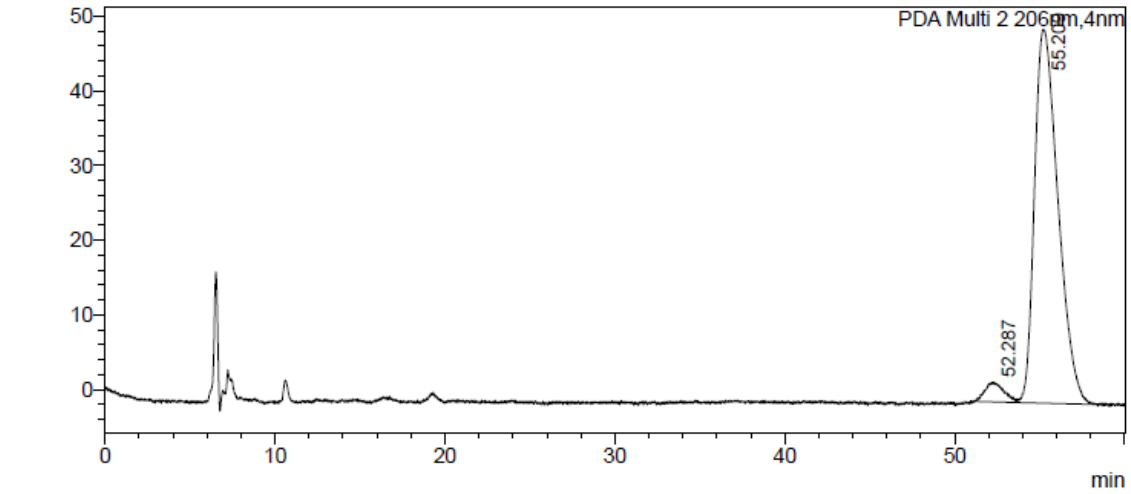


<Peak Table>

PDA Ch2 206nm

Peak#	Ret. Time	Area	Height	Area%
1	51.716	5444504	59483	49.609
2	55.073	5530379	55280	50.391
Total		10974883	114763	100.000

<Chromatogram>

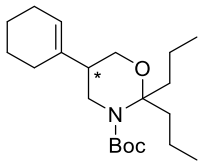


<Peak Table>

PDA Ch2 206nm

Peak#	Ret. Time	Area	Height	Area%
1	52.287	199299	2659	3.968
2	55.209	4823595	50106	96.032
Total		5022894	52765	100.000

<u>*tert*-butyl 5-(cyclohex-1-en-1-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate 4-3cu</u>



Chemical Formula: $C_{21}H_{37}NO_3$
Exact Mass: 351.2773

Obtained as colourless oil (68% yield) according to **General procedure B2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 5.52 – 5.38 (m, 1H), 3.83 (ddd, *J* = 31.9, 12.1, 6.2 Hz, 2H), 3.49 (dd, *J* = 11.5, 8.8 Hz, 1H), 3.07 (dd, *J* = 12.6, 11.1 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.13 – 1.84 (m, 7H), 1.74 – 1.52 (m, 5H), 1.45 (s, 9H), 1.43 – 1.27 (m, 4H), 0.90 (td, *J* = 7.4, 5.1 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2, 136.7, 122.6, 90.7, 79.7, 62.9, 43.7, 42.5, 39.3, 37.7, 28.6, 26.6, 25.3, 23.0, 22.5, 17.2, 16.4, 14.6, 14.5.

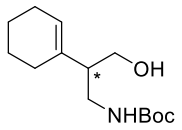
IR (neat): ν (cm^{-1}) 2929, 2362, 1692, 1392, 1164, 1104, 940, 786, 631.

HRMS (ESI): Calcd for $C_{21}H_{37}NNaO_3$ $[M+Na]^+$: 374.2666, found: 374.2664.

$[\alpha]_D^{20}$ = -10.7° (c = 1.23, $CHCl_3$).

The e.r. was determined by the corresponding amino alcohol.

<u>*tert*-butyl (2-(cyclohex-1-en-1-yl)-3-hydroxypropyl)carbamate</u>



Chemical Formula: $C_{14}H_{25}NO_3$
Exact Mass: 255.1834

^{1}H NMR (500 MHz, Chloroform-*d*) δ 5.48 (s, 1H), 4.67 (brs, 1H), 3.63 – 3.48 (m, 2H), 3.32 – 3.15 (m, 2H), 2.52 (brs, 1H), 2.22 – 2.13 (m, 1H), 2.06 – 1.97 (m, 2H), 1.96 – 1.88 (m, 2H), 1.65 – 1.51 (m, 4H), 1.44 (s, 9H).

^{13}C NMR (126 MHz, Chloroform-*d*) δ 156.9, 135.9, 124.5, 76.9, 62.0, 49.6, 40.0, 28.5, 27.1, 25.4, 23.0, 22.6.

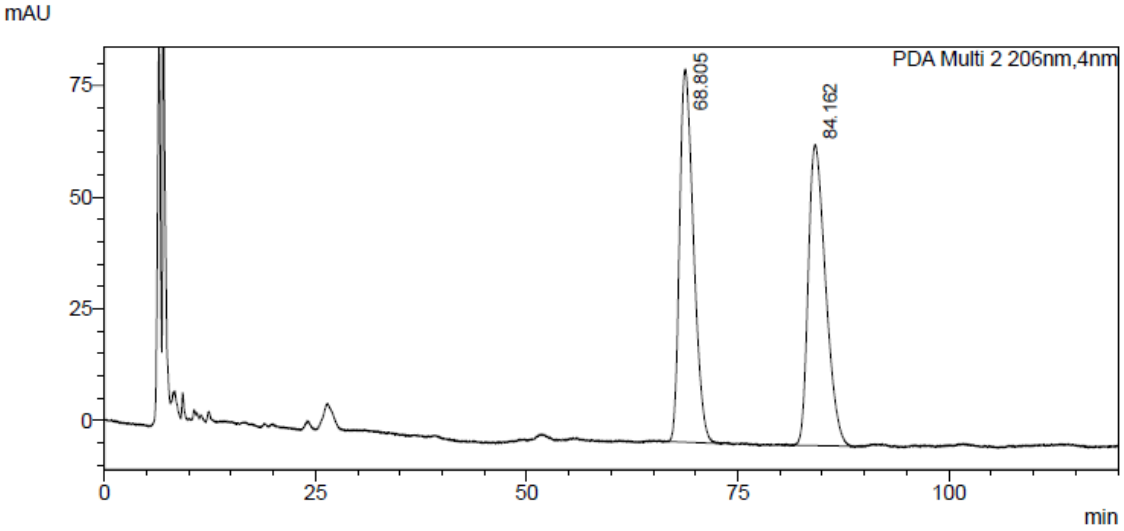
IR (neat): ν (cm^{-1}) 3357, 2928, 2361, 1687, 1510, 1366, 1250, 1168, 1040, 919, 863, 629.

HRMS (ESI): Calcd for $C_{14}H_{25}NNaO_3$ $[M+Na]^+$: 278.1727, found: 278.1723.

$[\alpha]_D^{20}$ = +8.2° (c = 1.31, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 0.5 mL/min, 206 nm, t_r(minor) = 69.1 min, t_r(major) = 84.7 min, 5:95 e.r.

<Chromatogram>

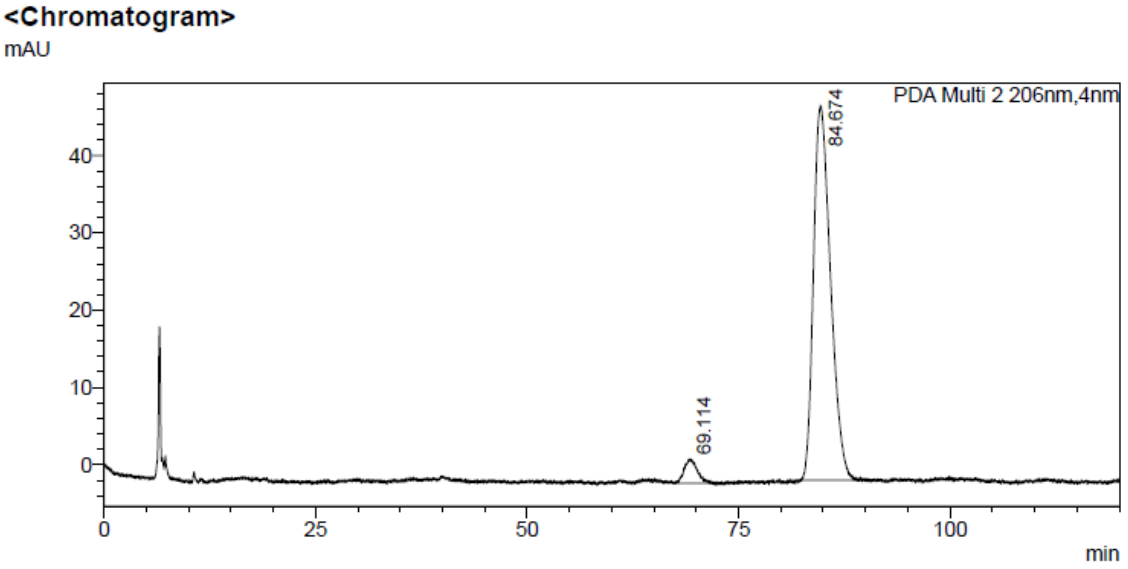


<Peak Table>

PDA Ch2 206nm

Peak#	Ret. Time	Area	Height	Area%
1	68.805	9572468	83534	49.923
2	84.162	9602109	67372	50.077
Total		19174577	150906	100.000

<Chromatogram>

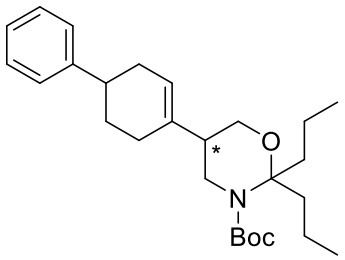


<Peak Table>

PDA Ch2 206nm

Peak#	Ret. Time	Area	Height	Area%
1	69.114	326837	3101	4.592
2	84.674	6791100	48545	95.408
Total		7117936	51647	100.000

tert-butyl 2,2-dipropyl-5-(1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-yl)-1,3-oxazinane-3-carboxylate 4-3cw



Chemical Formula: $C_{27}H_{41}NO_3$
Exact Mass: 427.3086

Obtained as colourless oil (47% yield) according to **General procedure B2** using (+)-sparteine (from R-OTf instead of R-Br).

The data shown below could be the mixture of diastereoisomers.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.33 – 7.27 (m, 2H), 7.24 – 7.17 (m, 3H), 5.57 (d, *J* = 3.6 Hz, 1H), 3.98 – 3.81 (m, 2H), 3.62 – 3.47 (m, 1H), 3.20 – 3.09 (m, 1H), 2.80 – 2.69 (m, 1H), 2.60 – 2.47 (m, 1H), 2.37 – 2.26 (m, 1H), 2.22 – 1.93 (m, 7H), 1.82 – 1.63 (m, 2H), 1.47 (s, 9H), 1.45 – 1.23 (m, 4H), 0.98 – 0.88 (m, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.2/154.2, 147.0/146.9, 136.7/136.6, 128.5, 127.0/126.9, 126.2, 122.4/122.3/122.2/122.2, 90.8/90.8, 79.8, 62.9/62.8, 43.9/43.5, 42.3/42.0, 40.2/40.0, 39.3/39.2, 37.8/37.6, 33.6/33.5, 30.1/30.0, 28.6, 27.2/27.2, 17.2/17.2, 16.4/16.4, 14.6, 14.5.

IR (neat): ν (cm^{-1}) 2960, 2361, 1690, 1392, 1163, 1103, 940, 787, 699, 631.

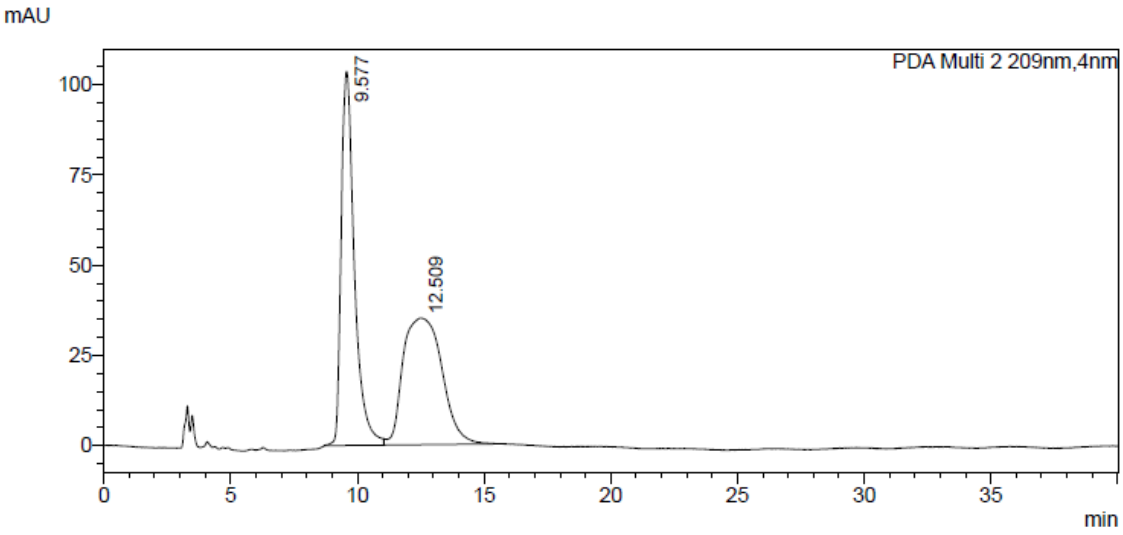
HRMS (ESI): Calcd for $C_{27}H_{41}NNaO_3$ $[M+Na]^+$: 450.2979, found: 450.2984.

$[\alpha]_D^{20}$ = -21.8° (c = 1.05, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.7:0.3, 1.0 mL/min, 209 nm, t_r(major) = 10.0 min, t_r(minor) = 13.9 min (?), 96:4 e.r.

(*The e.r. has to be checked. The minor peak is impurity or one of the diastereoisomers?*)

<Chromatogram>

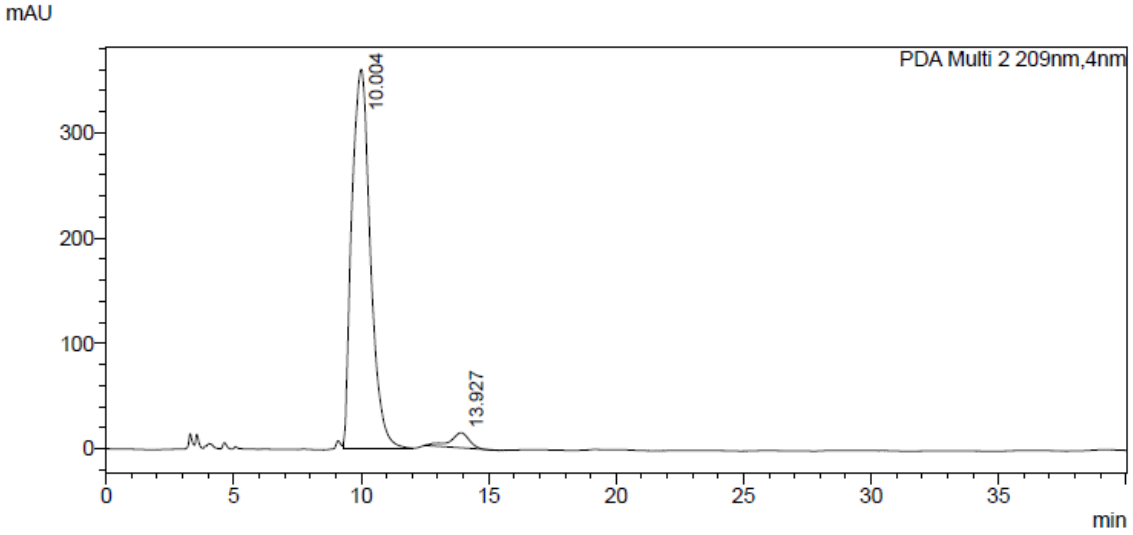


<Peak Table>

PDA Ch2 209nm

Peak#	Ret. Time	Area	Height	Area%
1	9.577	3757607	103601	49.994
2	12.509	3758447	35044	50.006
Total		7516053	138645	100.000

<Chromatogram>



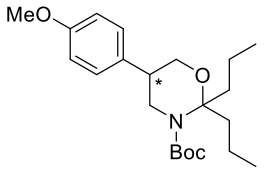
<Peak Table>

PDA Ch2 209nm

Peak#	Ret. Time	Area	Height	Area%
1	10.004	18272926	360483	96.079
2	13.927	745742	14391	3.921
Total		19018668	374875	100.000

Catalytic version of asymmetric deprotonation

<u>tert-butyl 5-(4-methoxyphenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate</u>

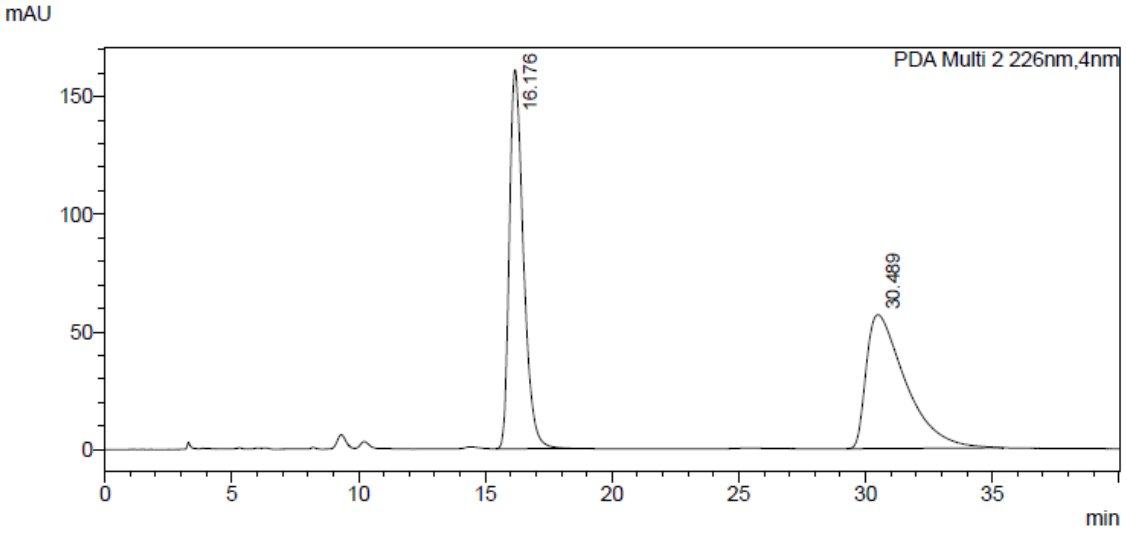


Chemical Formula: $C_{22}H_{35}NO_4$
Exact Mass: 377.2566

Obtained as colourless oil (68% yield) according to **General procedure B3** using catalytic (+)-sparteine surrogate.

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 226 nm, t_r(minor) = 16.4 min, t_r(major) = 30.2 min, 7:93 e.r.

<Chromatogram>

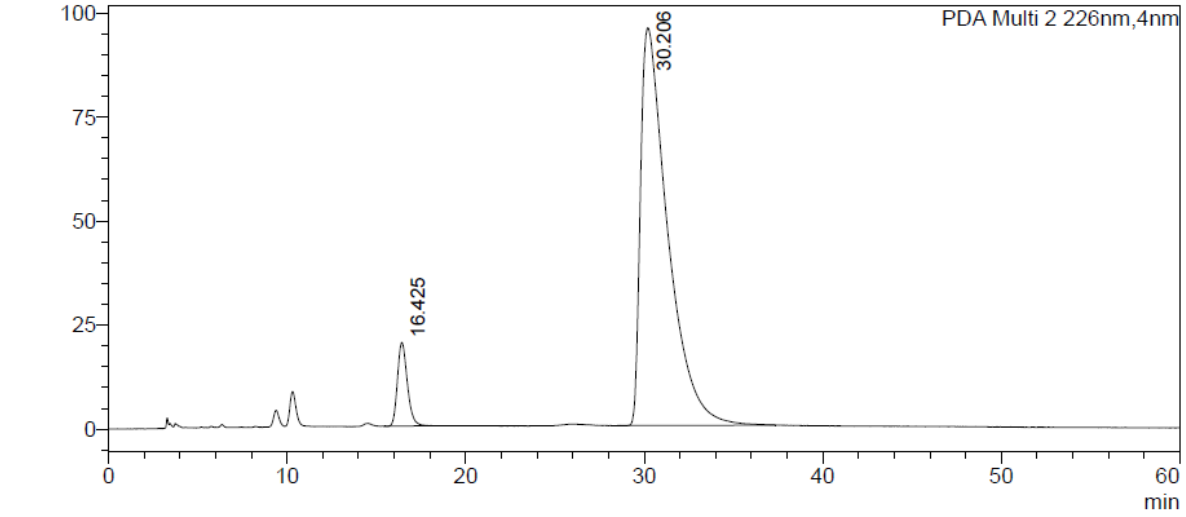


<Peak Table>

PDA Ch2 226nm

Peak#	Ret. Time	Area	Height	Area%
1	16.176	6214109	161123	50.339
2	30.489	6130381	56844	49.661
Total		12344490	217968	100.000

<Chromatogram>

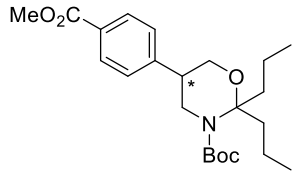


<Peak Table>

PDA Ch2 226nm

Peak#	Ret. Time	Area	Height	Area%
1	16.425	770302	20102	7.070
2	30.206	10125306	95609	92.930
Total		10895608	115711	100.000

<u>*tert*-butyl 5-(4-(methoxycarbonyl)phenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate</u>



Chemical Formula: $C_{23}H_{35}NO_5$
Exact Mass: 405.2515

Obtained as colourless oil (57% yield) according to **General procedure B3** using catalytic (+)-sparteine surrogate.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.00 – 7.95 (m, 2H), 7.34 – 7.28 (m, 2H), 4.09 – 4.00 (m, 2H), 3.88 (s, 3H), 3.71 (dd, *J* = 11.8, 7.9 Hz, 1H), 3.36 (dd, *J* = 12.8, 10.6 Hz, 1H), 3.26 – 3.15 (m, 1H), 2.20 – 2.02 (m, 3H), 1.82 – 1.71 (m, 1H), 1.55 – 1.47 (m, 1H), 1.44 (s, 9H), 1.42 – 1.24 (m, 3H), 0.92 (dt, *J* = 8.7, 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 166.9, 154.0, 147.0, 130.1, 129.0, 127.5, 91.1, 80.1, 64.5, 52.2, 45.3, 41.6, 39.0, 37.8, 28.5, 17.2, 16.4, 14.5, 14.4.

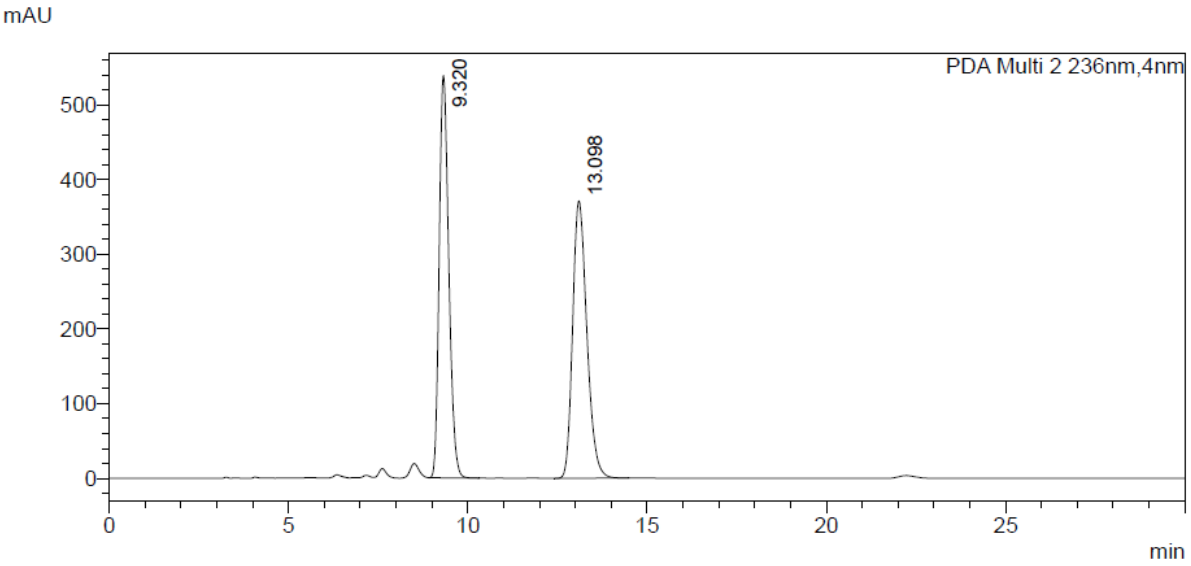
IR (neat): ν (cm^{-1}) 2960, 2362, 1689, 1392, 1280, 1168, 1109, 769, 632.

HRMS (ESI): Calcd for $C_{23}H_{35}NNaO_5$ $[M+Na]^+$: 428.2407, found: 428.2408.

$[\alpha]_D^{20}$ = -35.9° (c = 1.27, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 236 nm, t_r(major) = 9.3 min, t_r(minor) = 13.1 min, 94:6 e.r.

<Chromatogram>



<Peak Table>

PDA Ch2 236nm

Peak#	Ret. Time	Area	Height	Area%
1	9.320	9996438	538758	49.450
2	13.098	10218738	371201	50.550
Total		20215176	909959	100.000

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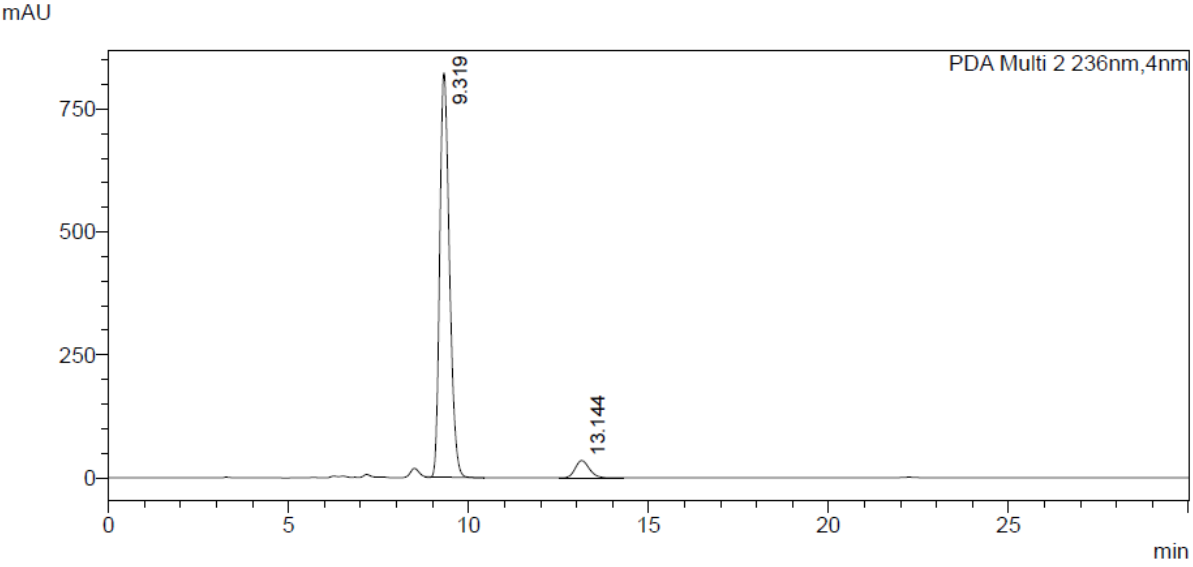
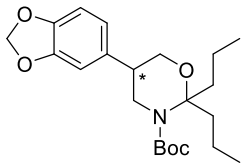


<Peak Table>

PDA Ch2 236nm

Peak#	Ret. Time	Area	Height	Area%
1	9.319	15436309	822701	94.220
2	13.144	946916	35021	5.780
Total		16383225	857722	100.000

<u>*tert*-butyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate</u>

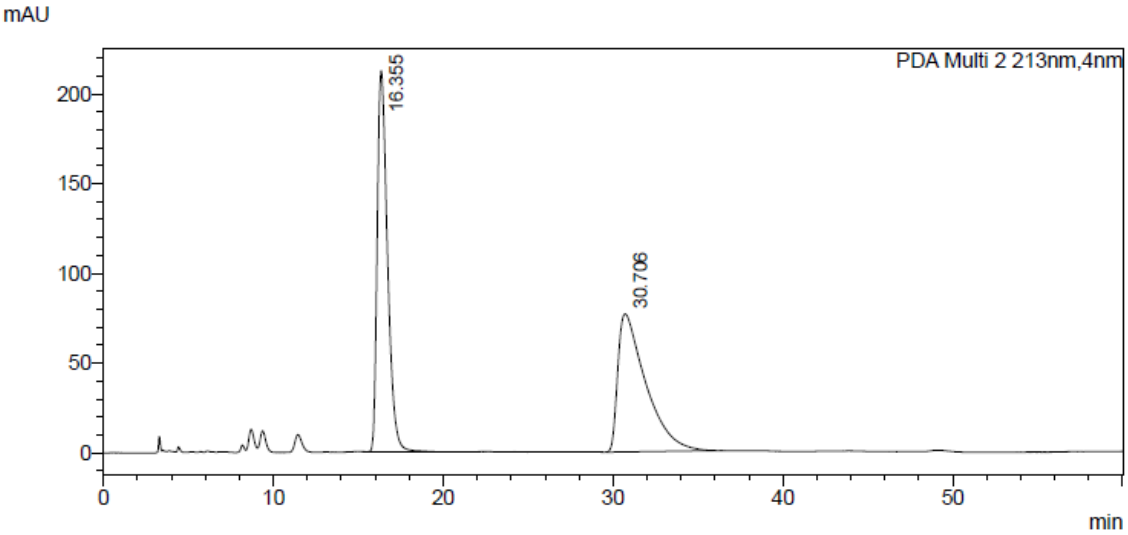


Chemical Formula: $C_{22}H_{33}NO_5$
Exact Mass: 391.2359

Obtained as colourless oil (73% yield) according to **General procedure B3** using catalytic (+)-sparteine surrogate.

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 213 nm, t_r(minor) = 14.2 min, t_r(major) = 28.4 min, 9:91 e.r.

<Chromatogram>

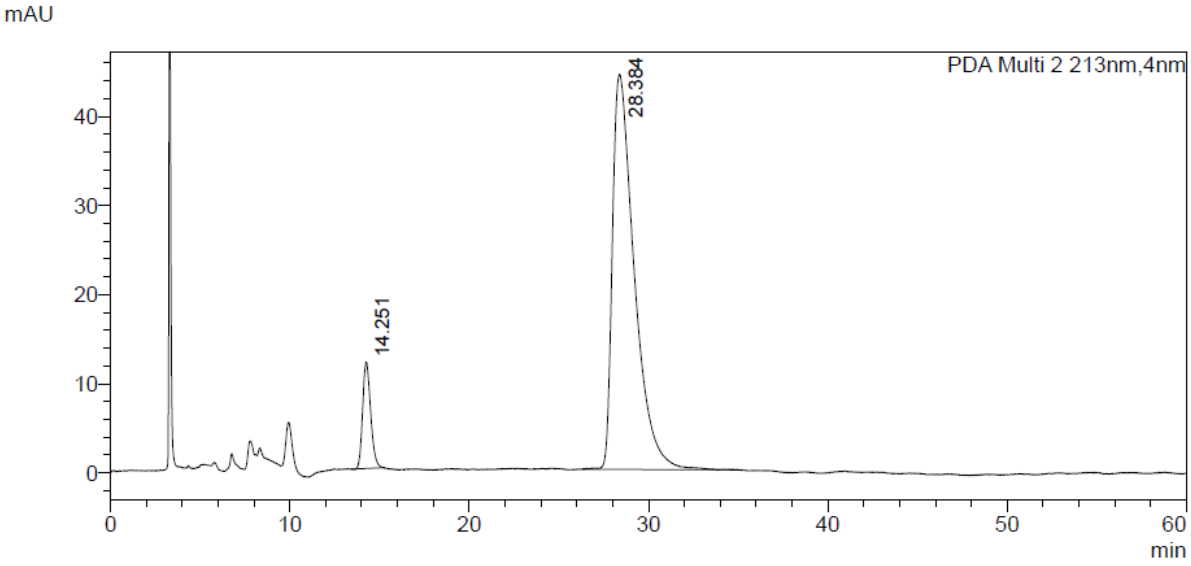


<Peak Table>

PDA Ch2 213nm

Peak#	Ret. Time	Area	Height	Area%
1	16.355	8934662	212326	50.444
2	30.706	8777520	76864	49.556
Total		17712181	289190	100.000

<Chromatogram>

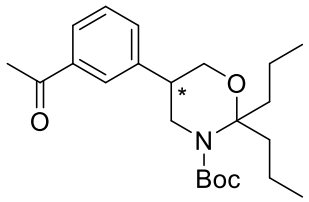


<Peak Table>

PDA Ch2 213nm

Peak#	Ret. Time	Area	Height	Area%
1	14.251	371065	11957	8.980
2	28.384	3761175	44351	91.020
Total		4132240	56308	100.000

***tert*-butyl 5-(3-acetylphenyl)-2,2-dipropyl-1,3-oxazinane-3-carboxylate**

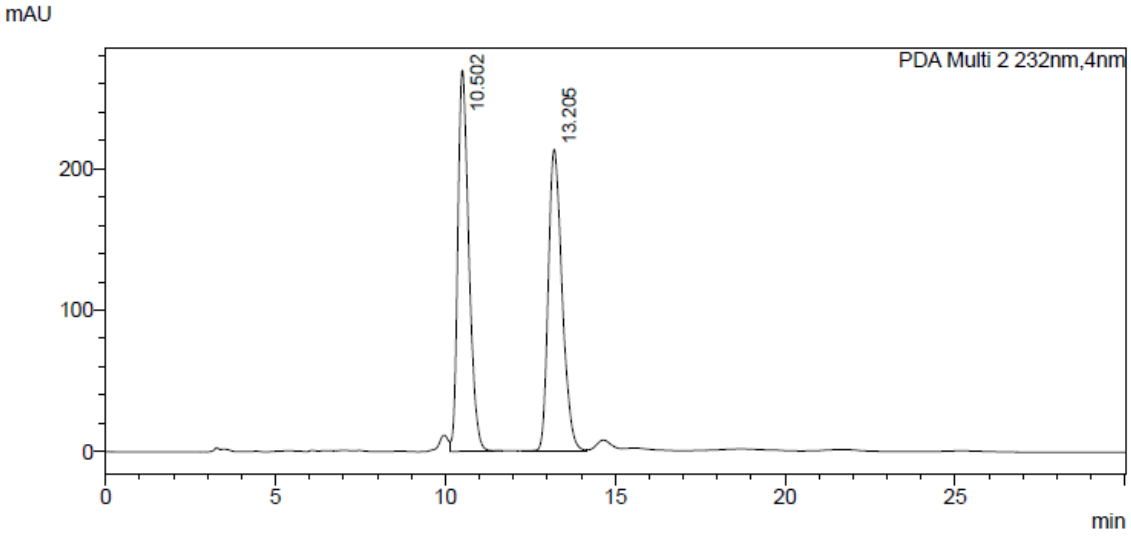


Chemical Formula: $C_{23}H_{35}NO_4$
Exact Mass: 389.2566

Obtained as colourless oil (26% yield) according to **General procedure B3** using catalytic (+)-sparteine surrogate.

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 232 nm, t_r(minor) = 10.3 min, t_r(major) = 12.3 min, 6:94 e.r.

<Chromatogram>

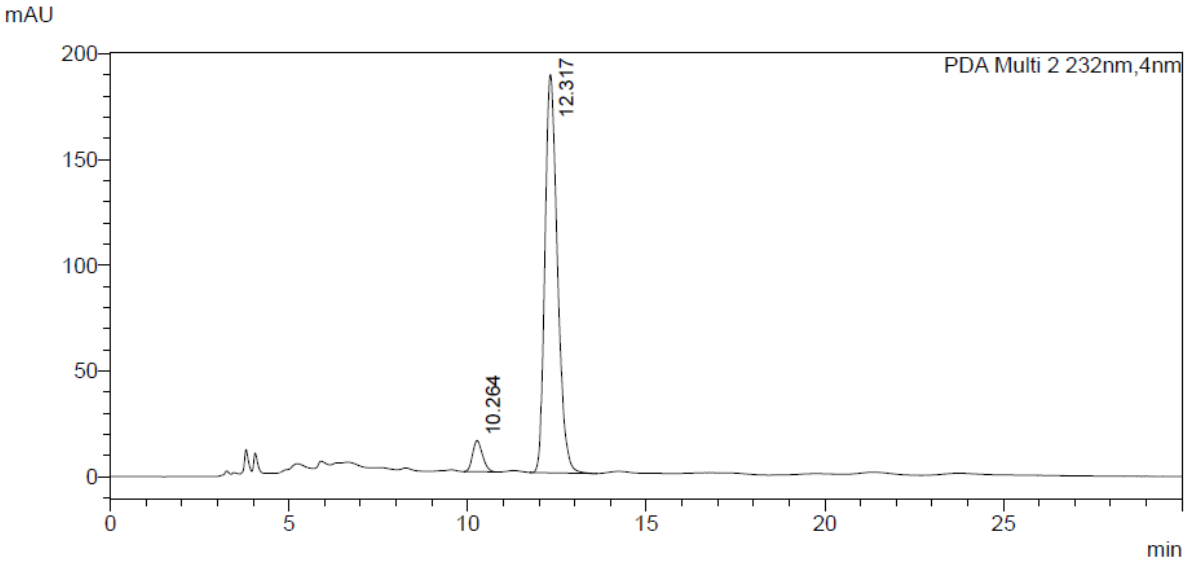


<Peak Table>

PDA Ch2 232nm

Peak#	Ret. Time	Area	Height	Area%
1	10.502	6091221	269284	50.307
2	13.205	6016836	212970	49.693
Total		12108058	482254	100.000

<Chromatogram>

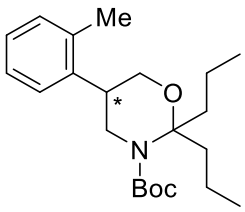


<Peak Table>

PDA Ch2 232nm

Peak#	Ret. Time	Area	Height	Area%
1	10.264	281776	14706	5.798
2	12.317	4578231	188294	94.202
Total		4860008	203000	100.000

***tert*-butyl 2,2-dipropyl-5-(o-tolyl)-1,3-oxazinane-3-carboxylate**



Chemical Formula: $C_{22}H_{35}NO_3$
Exact Mass: 361.2617

Obtained as colourless oil (52% yield) according to **General procedure B3** using (+)-sparteine surrogate.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.31 – 7.27 (m, 1H), 7.24 – 7.12 (m, 3H), 4.10 – 3.99 (m, 2H), 3.72 (dd, *J* = 11.6, 7.8 Hz, 1H), 3.44 – 3.28 (m, 2H), 2.36 (s, 3H), 2.23 – 2.09 (m, 3H), 1.86 – 1.74 (m, 1H), 1.59 – 1.51 (m, 1H), 1.47 (s, 9H), 1.43 – 1.26 (m, 3H), 0.96 (dt, *J* = 9.0, 7.4 Hz, 6H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.0, 140.0, 136.0, 130.6, 126.8, 126.6, 126.1, 91.0, 79.9, 64.4, 45.2, 39.2, 37.7, 37.4, 28.6, 19.7, 17.3, 16.5, 14.6, 14.5.

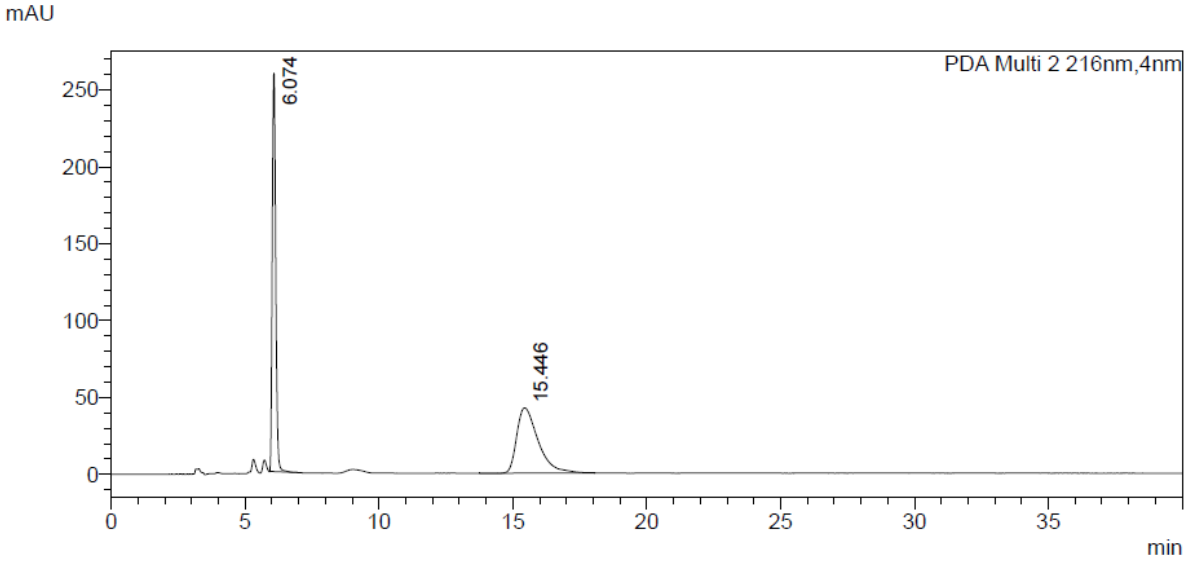
IR (neat): ν (cm^{-1}) 2960, 2361, 1690, 1458, 1392, 1167, 1098, 938, 755, 631.

HRMS (ESI): Calcd for $C_{22}H_{35}NNaO_3$ $[M+Na]^+$: 384.2509, found: 384.2514.

$[\alpha]_D^{20}$ = -7.8° (c = 1.28, $CHCl_3$).

HPLC separation: Chiralpak IC, *n*-Heptane/*i*-PrOH = 99.5:0.5, 1.0 mL/min, 220 nm, t_r(minor) = 6.1 min, t_r(major) = 12.9 min, 6:94 e.r.

<Chromatogram>

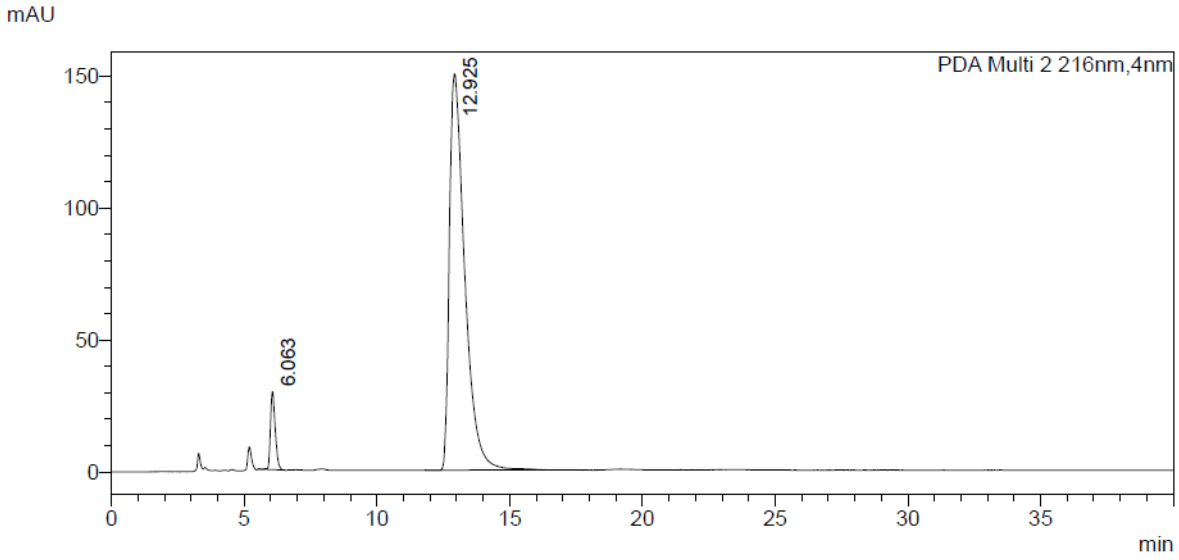


<Peak Table>

PDA Ch2 216nm

Peak#	Ret. Time	Area	Height	Area%
1	6.074	2333569	259142	49.764
2	15.446	2355708	42497	50.236
Total		4689277	301639	100.000

<Chromatogram>

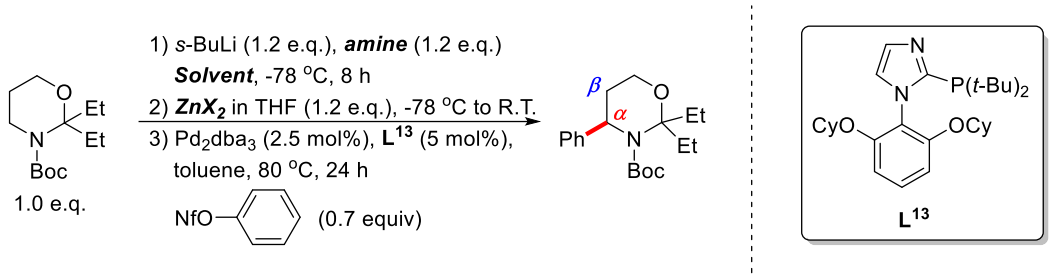


<Peak Table>

PDA Ch2 216nm

Peak#	Ret. Time	Area	Height	Area%
1	6.063	369024	29582	5.766
2	12.925	6031191	150221	94.234
Total		6400215	179803	100.000

C: *α-Arylation of N-Boc-tetrahydro-1,3-oxazine derivatives*



C1: *Racemic version*

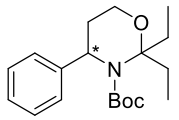
In a test-tube capped with rubber septum under argon, a solution of *N*-Boc-tetrahydro-1,3-oxazine (1.0 equiv., 0.5 mmol) and TMEDA (1.2 equiv.) in anhydrous THF (1.0 mL) was stirred and cooled to -78 °C (acetone/dry ice bath), and *s*-BuLi (1.2 equiv.) was added slowly via syringe. The reaction was stirred for 5 h at this temperature before a solution of $ZnCl_2$ in THF (0.5 M, 1.2 equiv.) was added dropwise. The mixture was stirred for 30 min at -78 °C and then warmed to room temperature and stirred for another 1 h. Solvents were removed *in vacuo*. Meanwhile, a solution of $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%) and **L^{13}** (5.0 mol%) in toluene (1.5 mL) was prepared and stirred at room temperature for 15 min. The catalyst solution was added to the organozinc reagent tube followed by the addition of aryl nonaflate (0.7 equiv.). The reaction mixture was then allowed to stir at 80 °C for 24 h. After cooling to room temperature, saturated NH_4Cl solution (2.0 mL) was added and the mixture was extracted twice with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel yielding the desired product.

C2: *Stoichiometric asymmetric version*

In a test-tube capped with rubber septum under argon, a solution of *N*-Boc-tetrahydro-1,3-oxazine (1.0 equiv., 0.5 mmol) and (+)-sparteine (1.2 equiv.) in anhydrous Et_2O (1.0 mL) was stirred and cooled to -78 °C (acetone/dry ice bath), and *s*-BuLi (1.2 equiv.) was added slowly via syringe. The reaction was stirred for 8 h at this temperature before a solution of $Zn(OAc)_2$ in THF (0.5 M, 1.2 equiv.) was added dropwise. The mixture was stirred for 30 min at -78 °C and then warmed to room temperature and stirred for another 1 h. Solvents were removed *in vacuo*. Meanwhile, a solution of $Pd_2dba_3{\cdot}CHCl_3$ (2.5 mol%) and **L^{13}** (5.0 mol%) in toluene (1.5 mL) was prepared and stirred at room temperature for 15 min. The catalyst solution was added to the organozinc reagent tube followed by the addition of aryl nonaflate (0.7 equiv.). The reaction mixture was then allowed to stir at 80 °C for 24 h.

After cooling to room temperature, saturated NH_4Cl solution (2.0 mL) was added and the mixture was extracted twice with ethyl acetate. The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel yielding the desired product.

<u>*tert*-butyl 2,2-diethyl-4-phenyl-1,3-oxazinane-3-carboxylate 4-4ba</u>



Chemical Formula: $C_{19}H_{29}NO_3$
Exact Mass: 319.2147

Obtained as colourless oil (61% yield) according to **General procedure C2** using (+)-sparteine.

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.50 – 7.45 (m, 2H), 7.33 – 7.27 (m, 2H), 7.24 – 7.18 (m, 1H), 5.29 (dd, *J* = 6.3, 3.3 Hz, 1H), 3.98 – 3.83 (m, 2H), 2.43 – 2.30 (m, 1H), 2.29 – 2.15 (m, 3H), 2.14 – 2.04 (m, 1H), 1.77 (dq, *J* = 14.6, 7.3 Hz, 1H), 1.38 (s, 9H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.64 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR (101 MHz, Chloroform-*d*) δ 154.4, 144.6, 128.1, 127.4, 126.6, 92.3, 80.0, 56.4, 53.8, 30.3, 28.9, 28.5, 28.3, 8.9, 8.3.

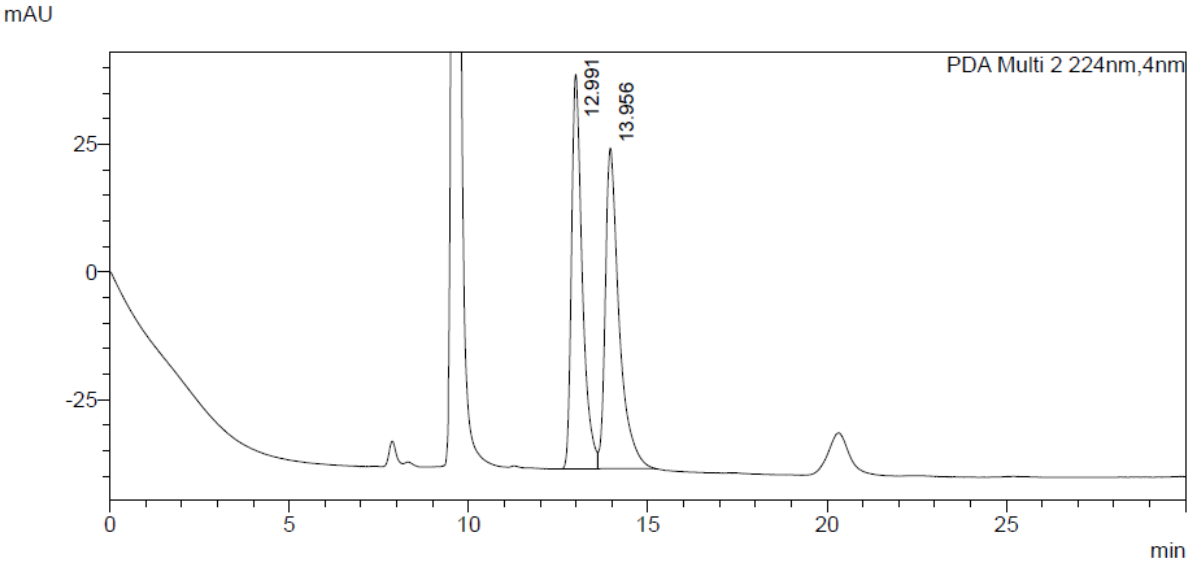
IR (neat): ν (cm^{-1}) 2958, 2361, 1686, 1455, 1366, 1254, 1168, 1098, 890, 700, 629.

HRMS (ESI): Calcd for $C_{19}H_{29}NNaO_3$ $[M+Na]^+$: 342.2040, found: 342.2042.

$[\alpha]_D^{20}$ = -50.2° (c = 0.85, $CHCl_3$).

HPLC separation: Chiralpak IA, *n*-Heptane/*i*-PrOH = 100:0, 0.4 mL/min, 224 nm, t_r(minor) = 11.9 min, t_r(major) = 12.8 min, 3:97 e.r.

<Chromatogram>

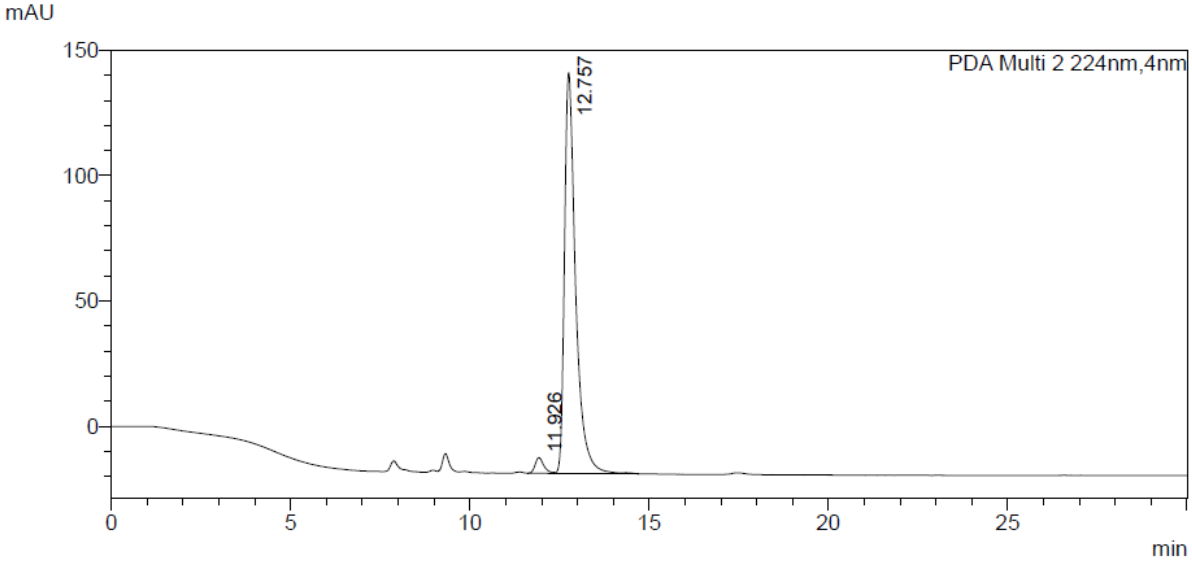


<Peak Table>

PDA Ch2 224nm

Peak#	Ret. Time	Area	Height	Area%
1	12.991	1611032	77195	48.910
2	13.956	1682820	62744	51.090
Total		3293852	139939	100.000

<Chromatogram>



<Peak Table>

PDA Ch2 224nm

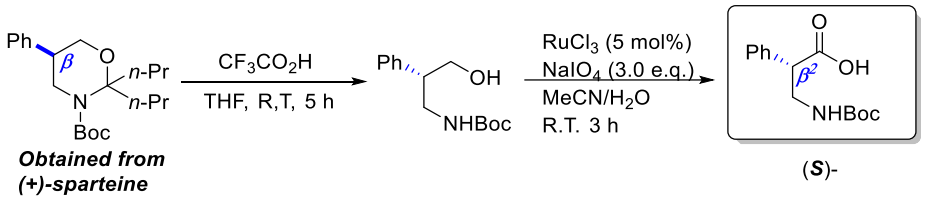
Peak#	Ret. Time	Area	Height	Area%
1	11.926	106111	6259	2.987
2	12.757	3446390	159825	97.013
Total		3552501	166084	100.000

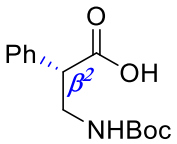
D: ***Synthesis of Enantiopure β²-amino acid derivatives***

D1[100]: To a solution of *β*-arylated product in THF (0.1 M) was added 50% aqueous trifluoroacetic acid under ice-batch temperature. After 1 h, the reaction temperature was allowed to increase to room temperature and the solution was stirred until the starting material was not detectable (TLC). The mixture was dissolved in 10 mL of water and extracted with ethyl ether. The combined organic extracts were dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The residue was purified by a short pad of flash column chromatography with ethyl acetate/hexane as an eluent.

D2: To a solution of the amino alcohol (1.0 equiv.) in the mixture of $MeCN/H_2O$ was added $RuCl_3$ hydrate (5 mol%) and $NaIO_4$ (3.0 equiv.) at 0 °C. The reaction mixture was then allowed to warm to room temperature for 3.0 h. The mixture was quenched by 5 mol% Na_2CO_3 aqueous solution and extracted with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous $NaSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/methanol as an eluent.

(*S*)-3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid





Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314

The amino acid was obtained as white solid (57% yield over two steps). The e.r. was determined by the corresponding methylation product.[158]

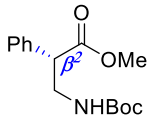
The configuration was determined to be ***S***- by comparing the $[\alpha]_D^{20}$ reported in the literature.[158]

^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 – 7.26 (m, 5H), 6.94 (brs, 0.5H), 4.96 (brs, 0.5H), 3.92 (brs, 0.5H), 3.80 (brs, 0.5H), 3.68 – 3.43 (m, 2H), 1.48 (brs, 4.5H), 1.42 (brs, 4.5H).

The ^{1}H-NMR is consistent with the reported data.[158]

[α]$_D^{20}$ = -63.5° (c = 0.92, $CHCl_3$).

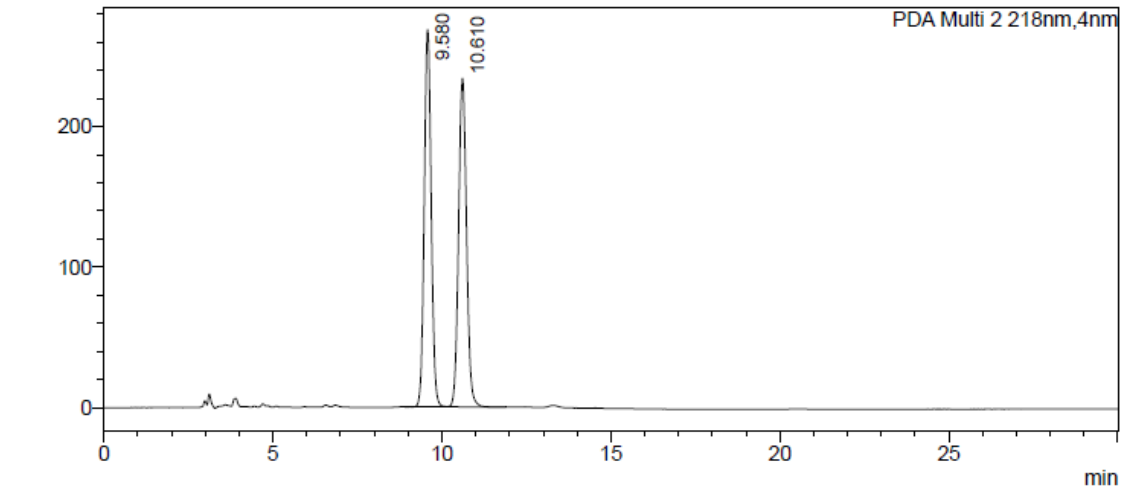
Reported in the literature: **[α]$_D^{20}$** = -86° (c = 1.25, $CHCl_3$) for *S* isomer, 99% ee.[159]



Chemical Formula: $C_{15}H_{21}NO_4$
Exact Mass: 279.1471

HPLC separation: Chiralpak AD-H, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, t_r(minor) = 7.5 min, t_r(major) = 8.5 min, 3:97 e.r.

<Chromatogram>



<Peak Table>

PDA Ch2 218nm

Peak#	Ret. Time	Area	Height	Area%
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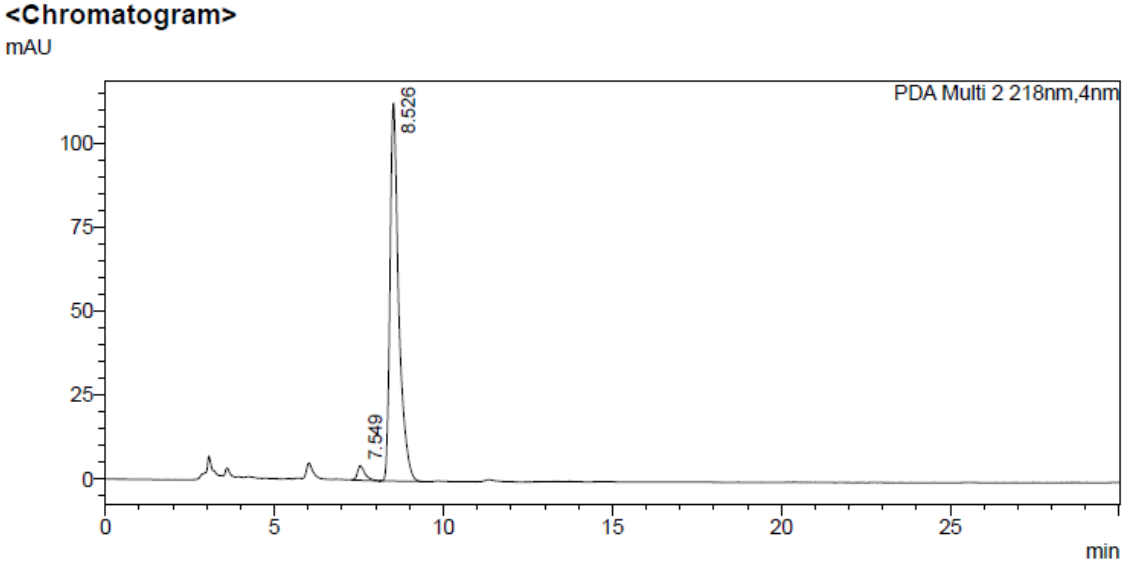
2	10.610	3835959	233719	50.024
Total		7668209	501970	100.000

<Chromatogram>

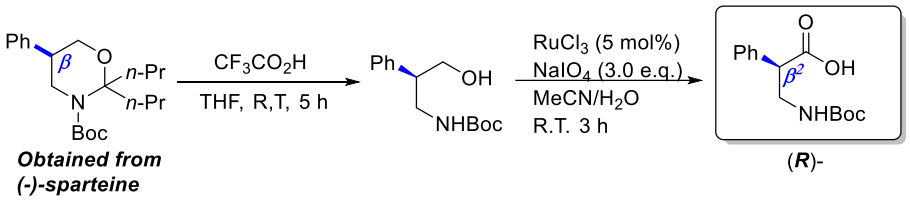


<Peak Table>

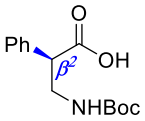
PDA Ch2 218nm

Peak#	Ret. Time	Area	Height	Area%
1	7.549	67059	4392	3.214
2	8.526	2019469	112568	96.786
Total		2086529	116959	100.000

(*R*)-3-((*tert*-butoxycarbonyl)amino)-2-phenylpropanoic acid

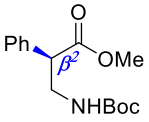


Obtained from (-)-sparteine



Chemical Formula: $C_{14}H_{19}NO_4$
Exact Mass: 265.1314

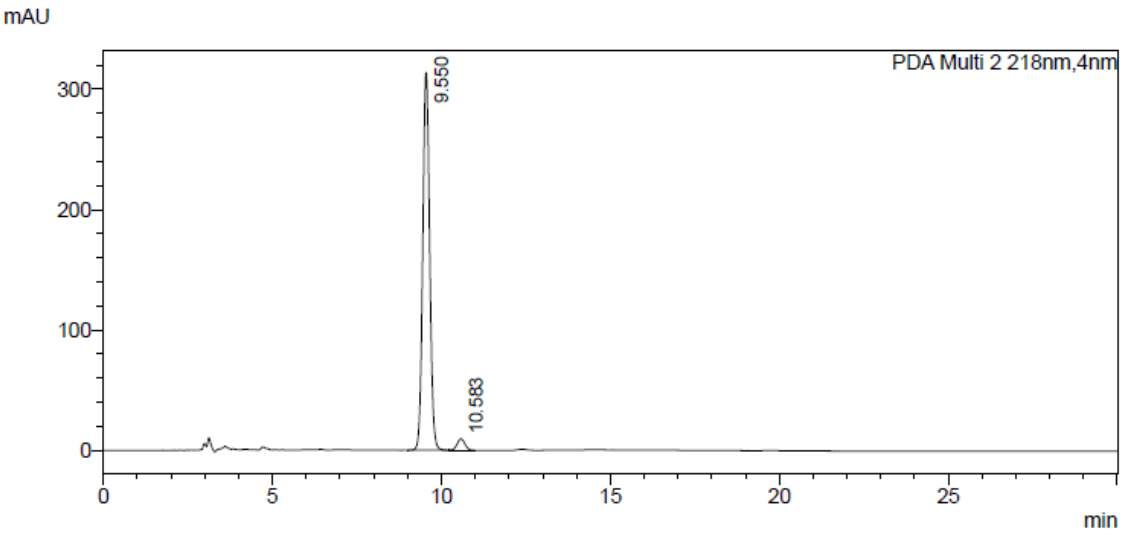
The amino acid was obtained as white solid (61% yield over two steps). The e.r. was determined by the corresponding methylation product.[159]



Chemical Formula: $C_{15}H_{21}NO_4$
Exact Mass: 279.1471

HPLC separation: Chiralpak AD-H, *n*-Heptane/*i*-PrOH = 95:5, 1.0 mL/min, 218 nm, t_r(minor) = 9.6 min, t_r(major) = 10.6 min, 97:3 e.r.

<Chromatogram>



<Peak Table>

PDA Ch2 218nm

Peak#	Ret. Time	Area	Height	Area%
1	9.550	4449316	313695	96.695
2	10.583	152094	9518	3.305
Total		4601410	323213	100.000

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Curriculm vitae

Ke-Feng Zhang

Born: 01/09/1988, Anhui Province, P. R. China

Education

2015.09- present	**Ph.D.** in Organic Chemistry, University of Basel, Switzerland ***Supervisor***: Prof. Olivier Baudoin
2014.10-2015.08	**Ph.D.** in Organic Chemistry, Université Claude Bernard Lyon 1, France ***Supervisor***: Prof. Olivier Baudoin
2011.09-2014.06	**M.Sc.** in Chemistry, Tianjin University, P.R. China ***Supervisor***: Prof. Yan Zheng and Prof. Jun-An Ma
2007.09-2011.06	**B.Sc.** in Applied Chemistry, Huaibei Normal University, P.R. China

Academic Activities

- 1st International Symposium on Catalysis for Sustainable Chemical Synthesis, 2017, Freiburg, Germany (Poster Presentation);
- Swiss Chemical Society (SCS) Fall meeting, 2017, Bern, Switerland (Poster Presentation);
- 37th Regio-Symposium, 2017, Liestal, Switerland (Poster Presentation);
- 18th Tetrahedron Symposium, 2017, Budapest, Hungary (Poster Presentation);
- 1st Swiss Industrial Chemistry Symposium, 2016, Basel, Switzerland (Poster Presentation);
- Swiss Chemical Society (SCS) Fall meeting, 2016, Zurich, Switerland (Poster Presentation);
- 36th Regio-Symposium, 2016, Colmar, France (Oral and Poster Presentation);
- 35th Regio-Symposium, 2015, Falkau, Germany;

Awards

- 2017 Chemistry Travel Award Supported by SCNAT and SCS
- 2016 Best Poster Award at 1st Swiss Industrial Chemistry Symposium

Publication List

1. **Ke-Feng Zhang**, Fadri Christoffel, and Olivier Baudoin* "Barbier-Negishi Coupling of Secondary Alkyl Bromides with Aryl and Alkenyl Triflates and Nonaflates" *Angew. Chem. Int. Ed.* **2018**, *57*, 1982-1986 (Highlight by *Synfacts*, **2018**, 14, 411).

2. Stéphanie Dupuy[†], **Ke-Feng Zhang**[†], Anne-Sophie Goutierre and Olivier Baudoin[*] "Terminal-Selective Functionalization of Alkyl Chains by Regioconvergent Cross-Coupling" *Angew. Chem. Int. Ed.* **2016**, *55*, 14793–14797. ([†] **Co-first author**)

3. **Ke-Feng Zhang**, Feng Li, Jing Nie and Jun-An Ma* "Asymmetric Cooperative Catalysis in the Conjugate Addition of Pyrazolones to Nitroolefins and Sequential Dearomative Chlorination" *Sci China Chem.* **2014**, *57*, 265–275.

4. **Ke-Feng Zhang**, Jing Nie, Ran Guo, Yan Zheng and Jun-An Ma* "Chiral Phosphoric Acid-Catalyzed Asymmetric Aza-Friedel-Crafts Reaction of Indoles with Cyclic *N*-Acyl Ketimines: Highly Enantioselective Synthesis of Trifluoromethyl Dihydroquinazolines" *Adv. Synth. Catal.* **2013**, *355*, 3497–3502.

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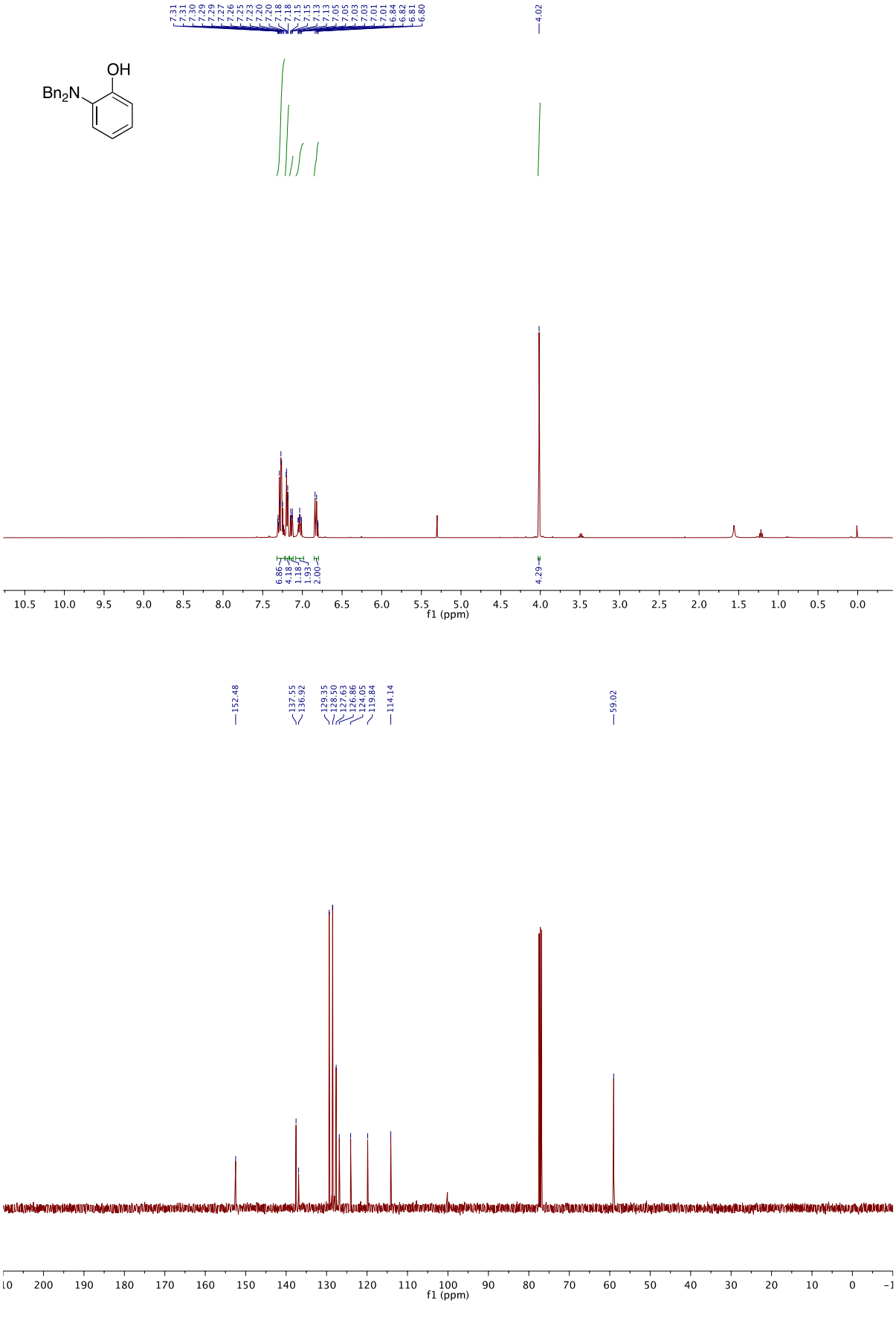
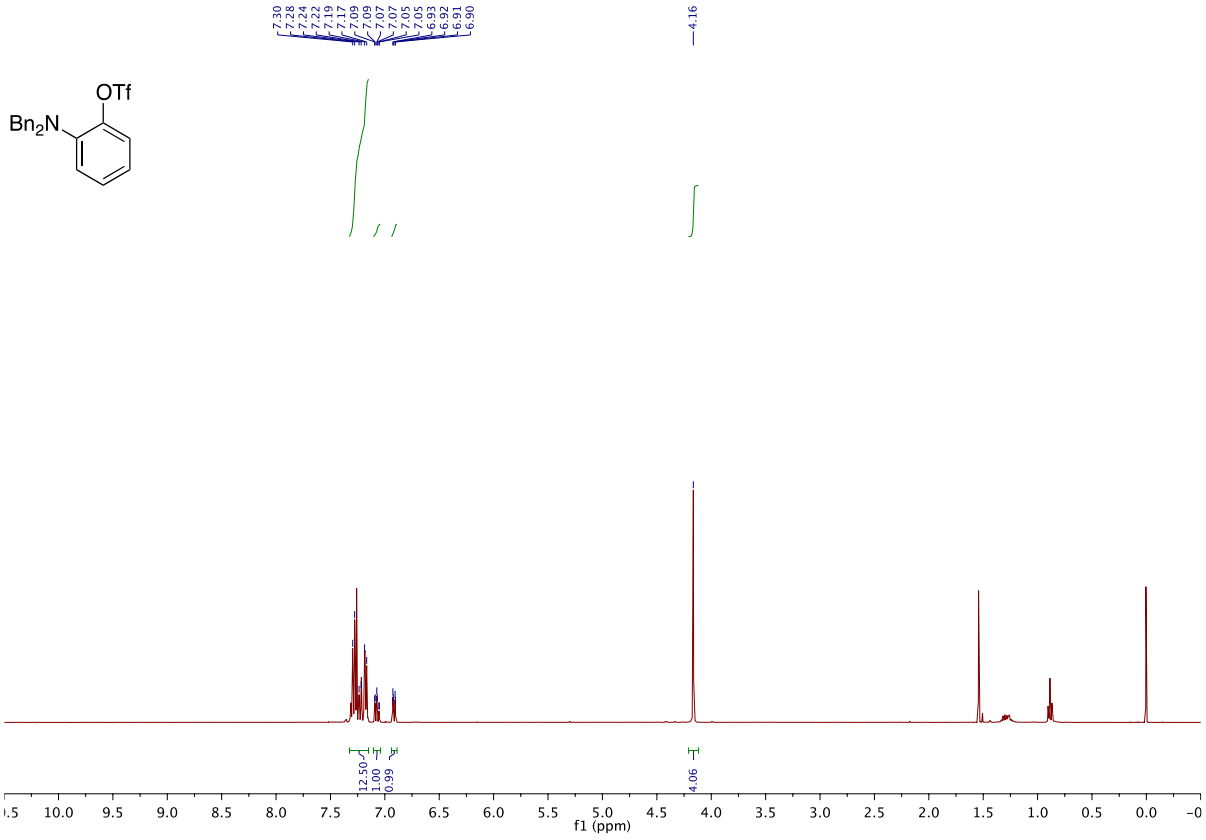
Spectra for compounds

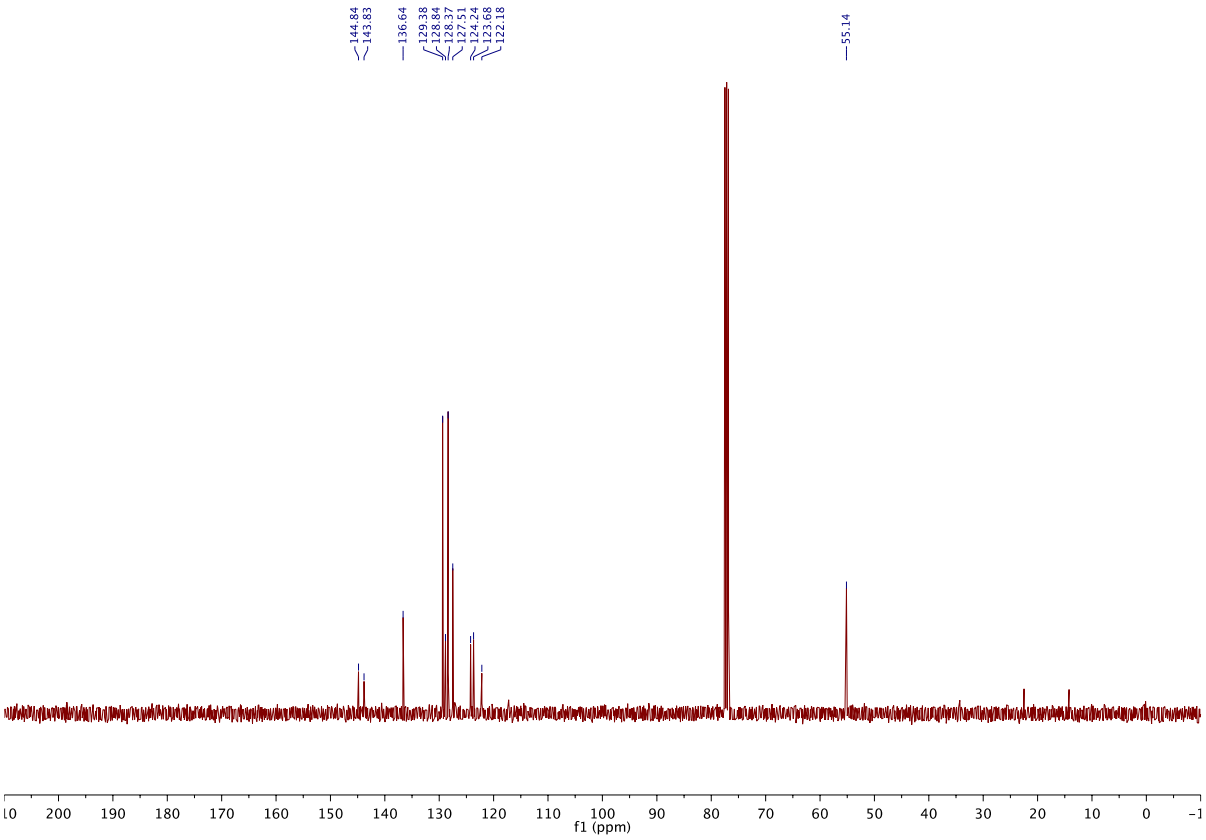
Chapter 2

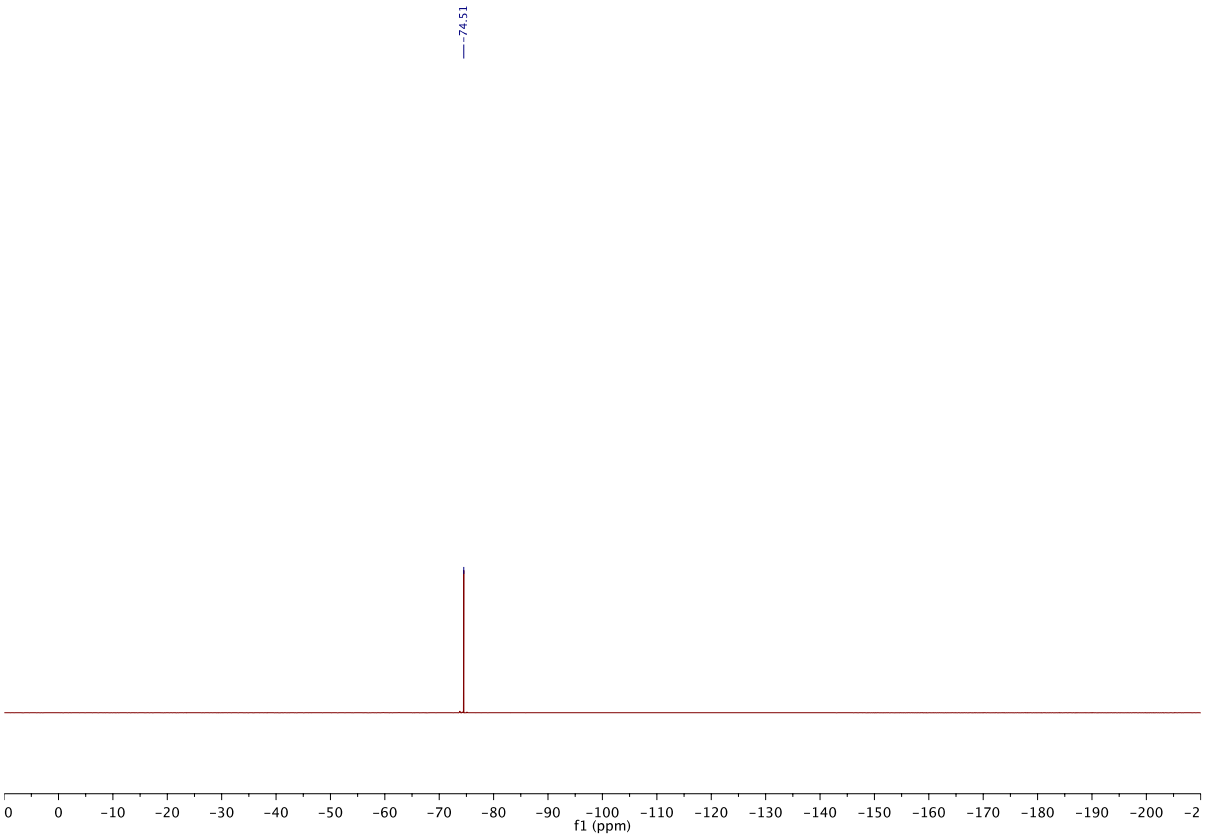
2-(dibenzylamino)phenol



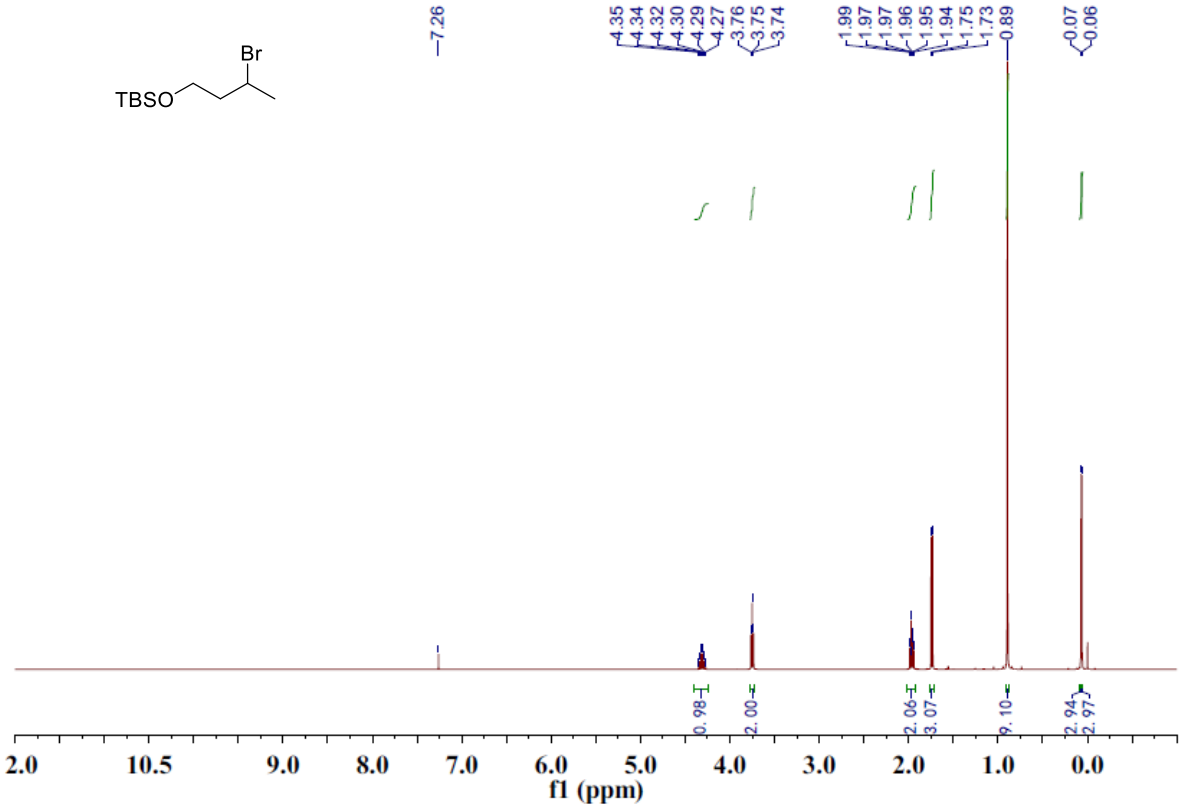
2-(dibenzylamino)phenyl trifluoromethanesulfonate

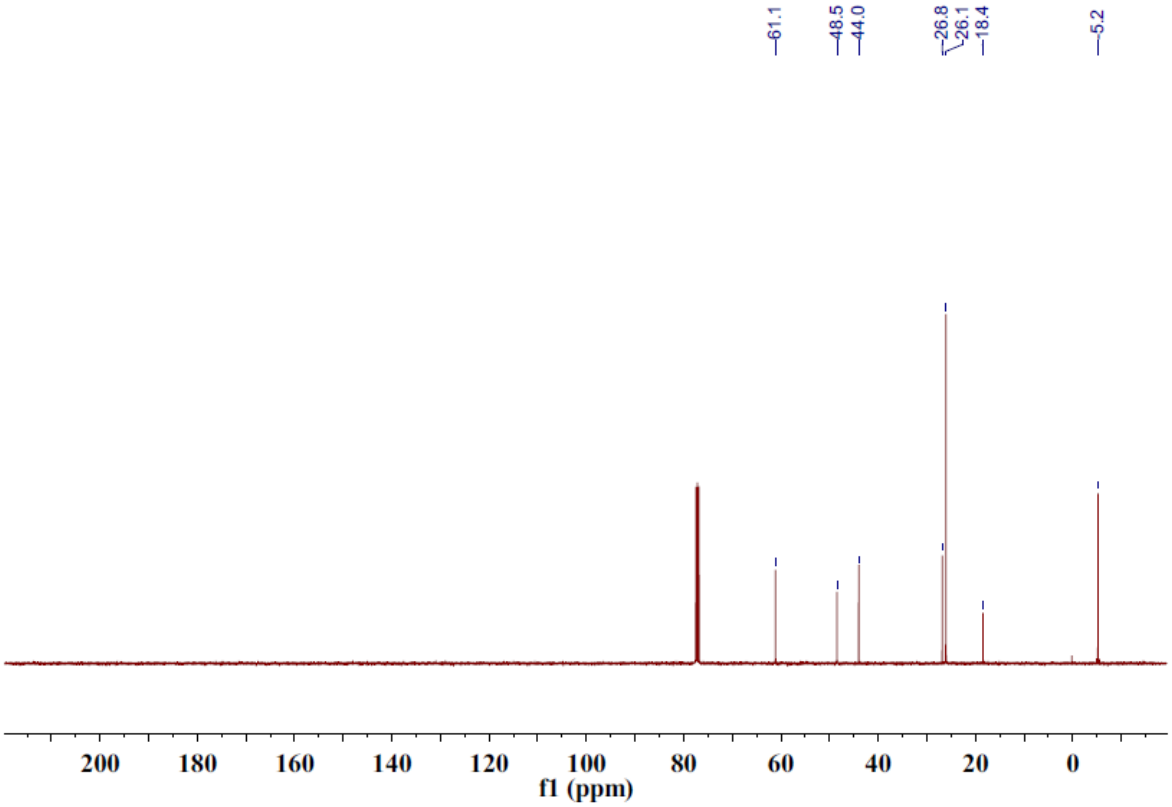






3-(Bromobutoxy)-*tert*-butyldimethylsilane





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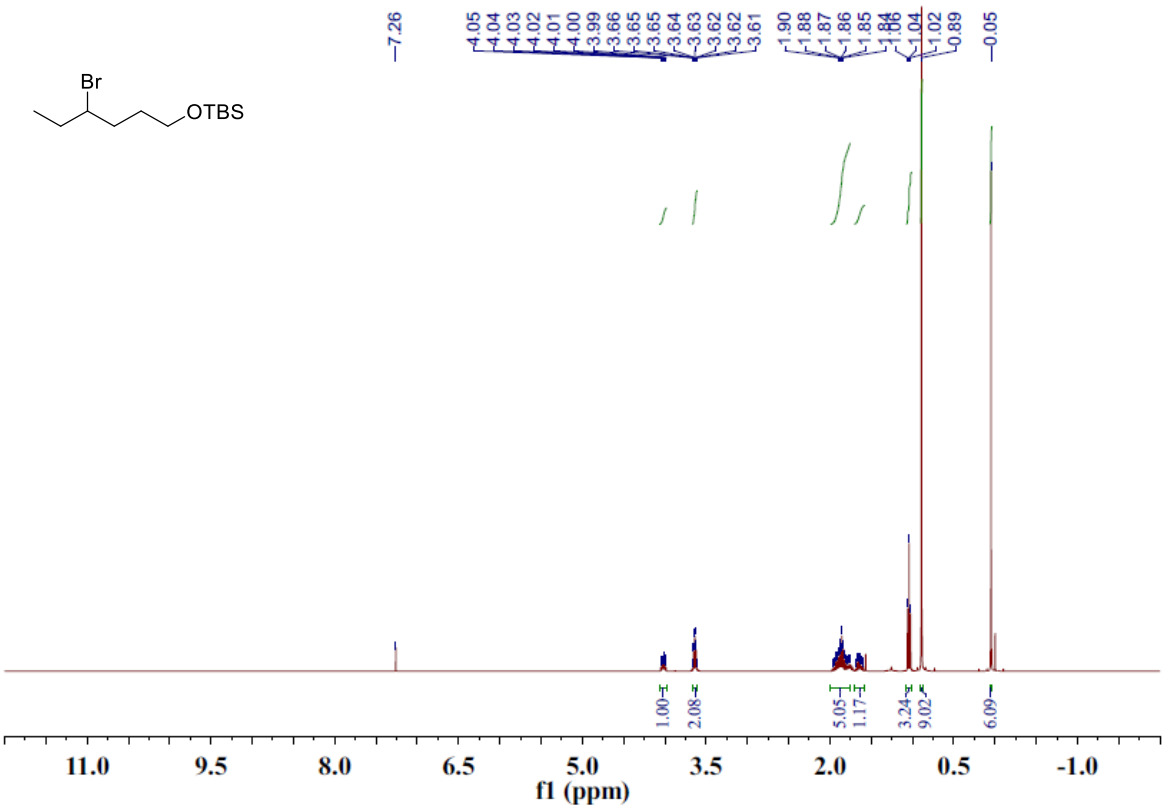

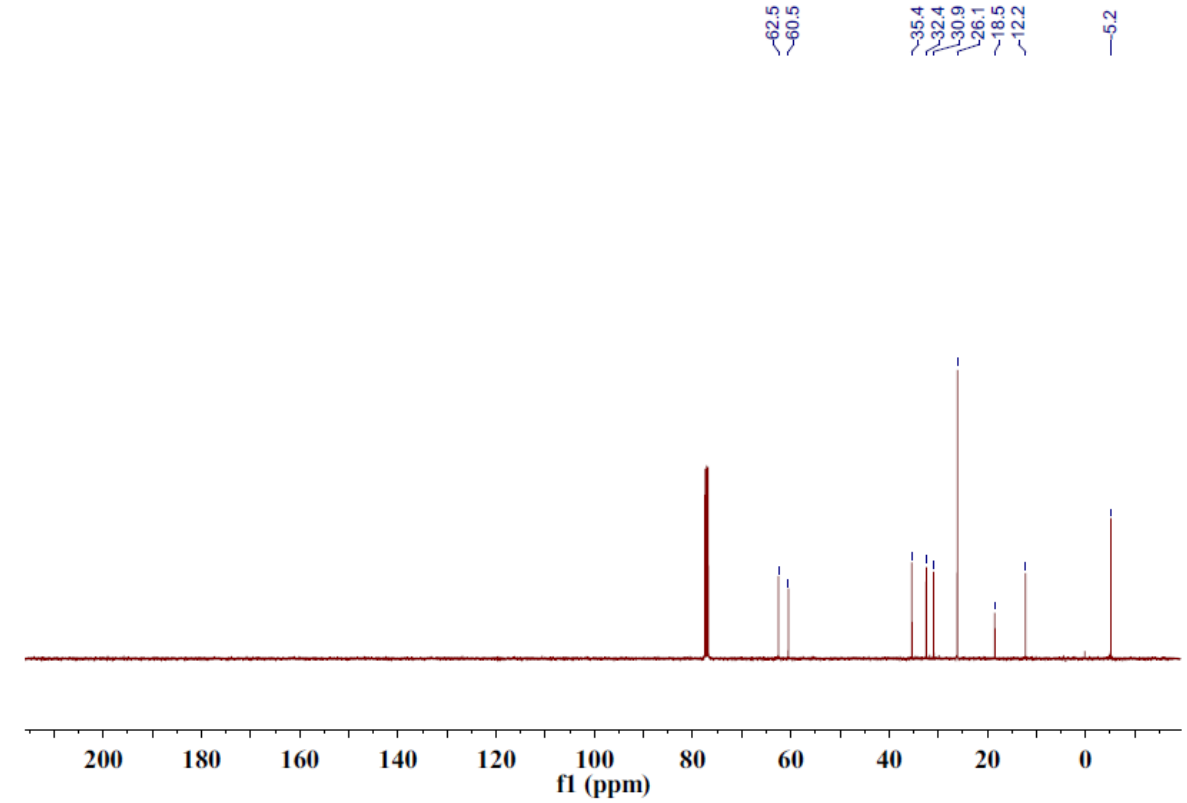

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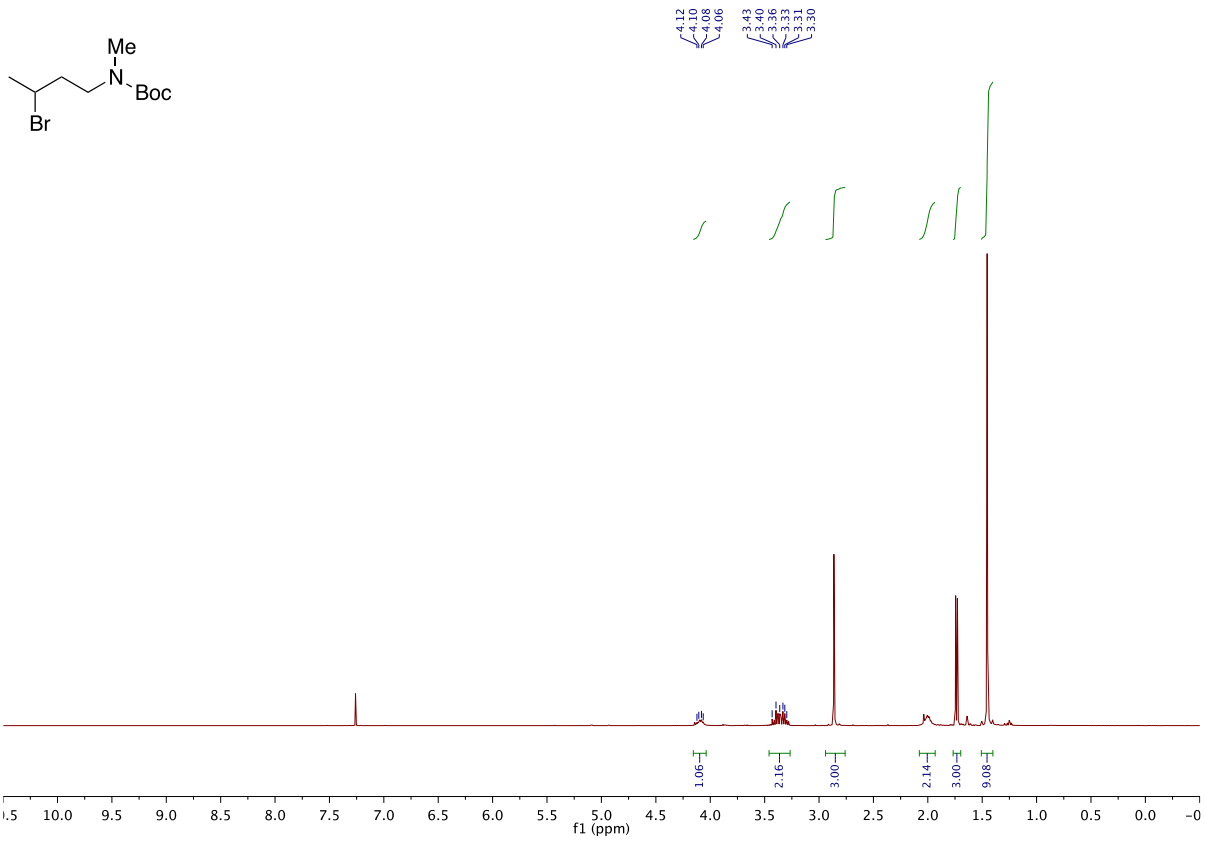

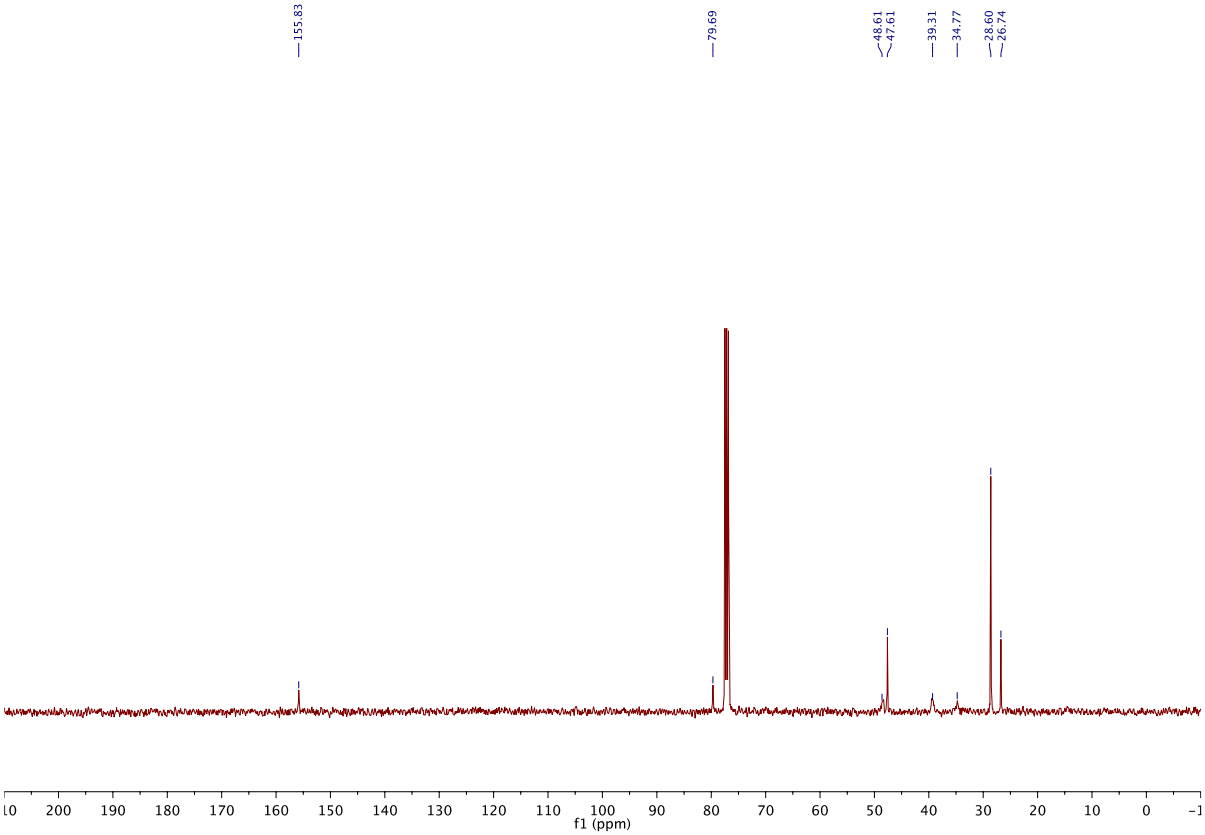

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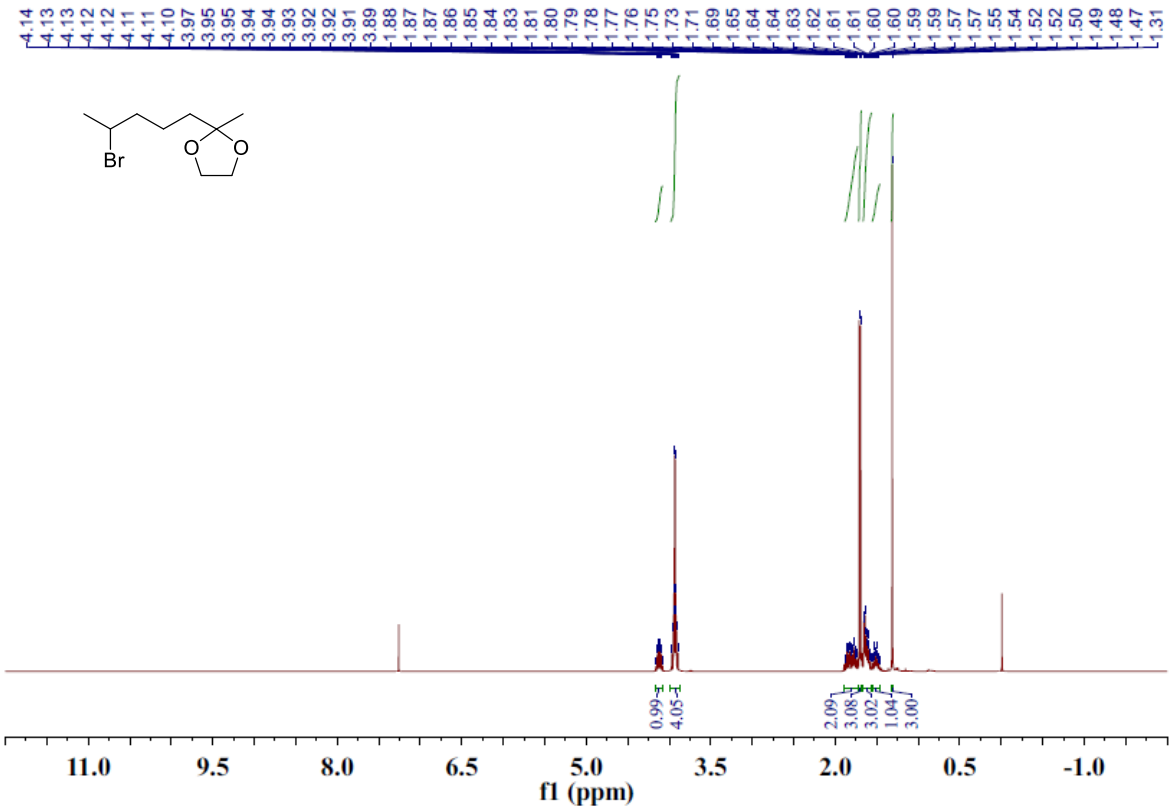

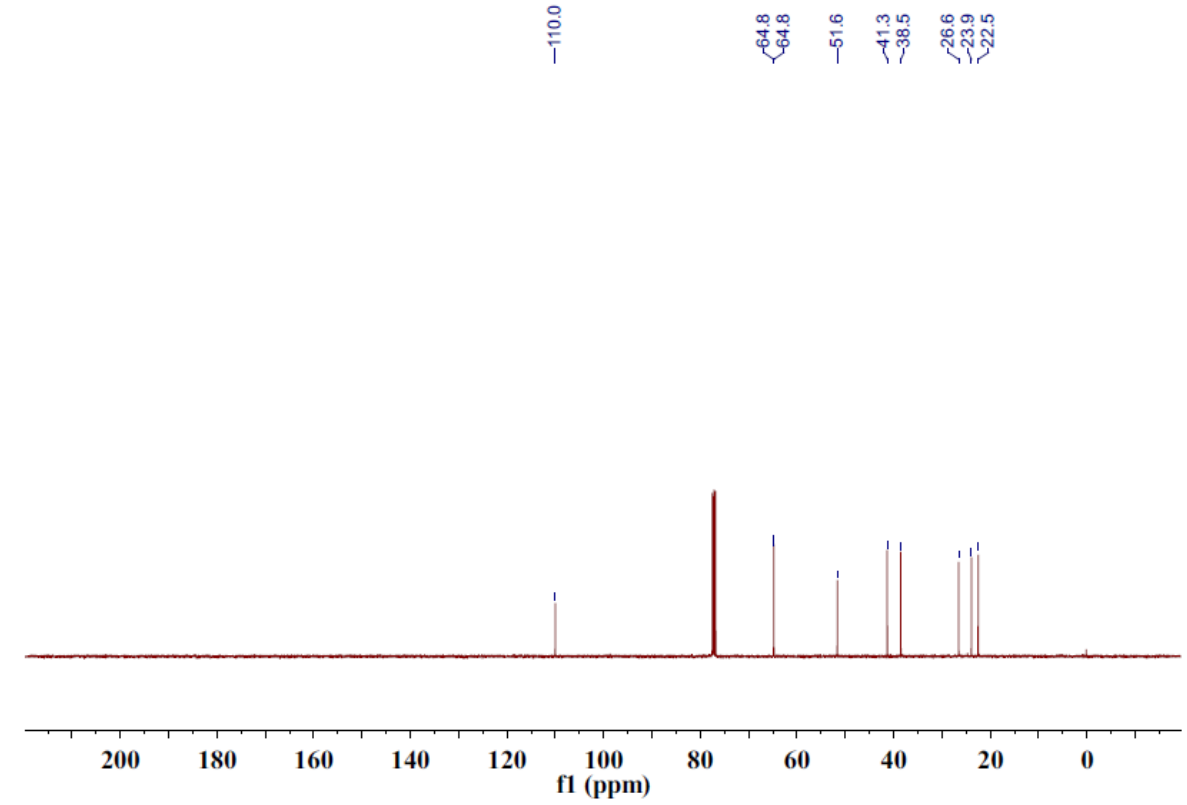

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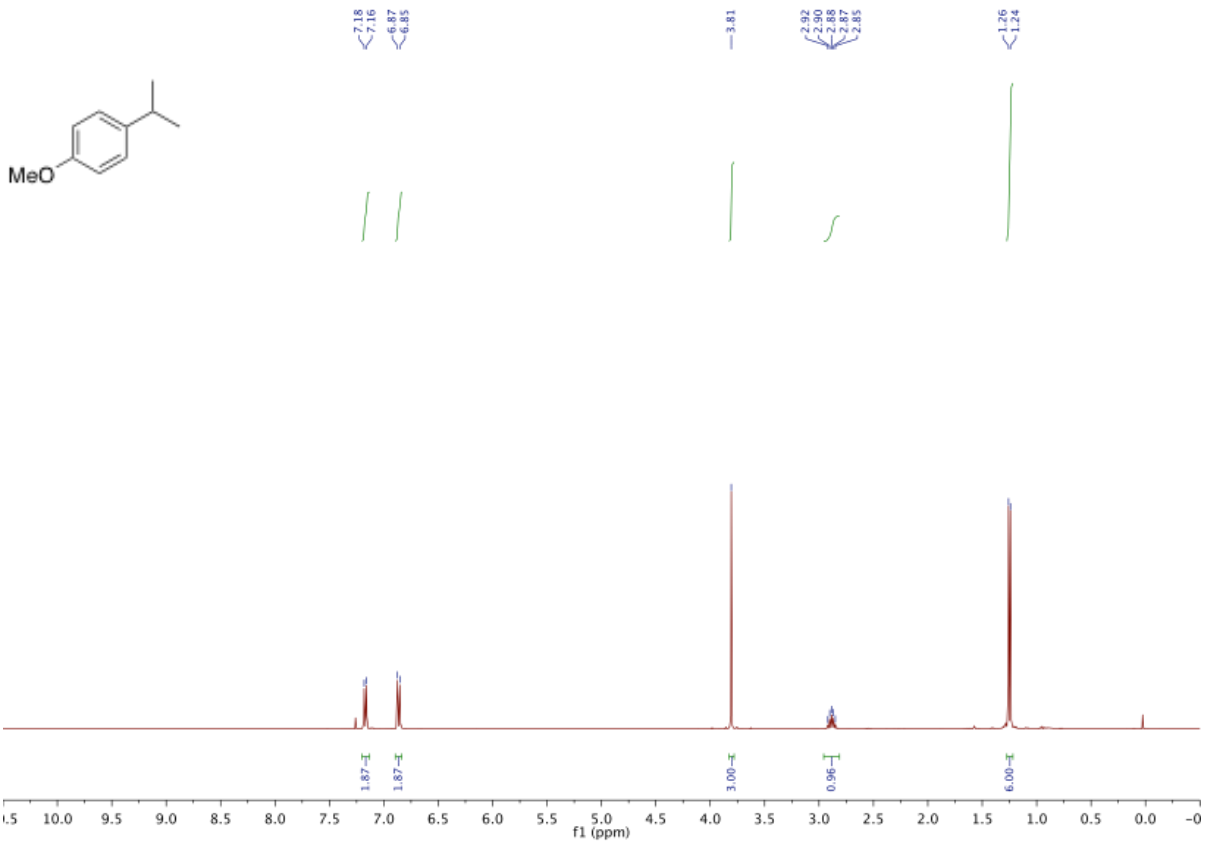

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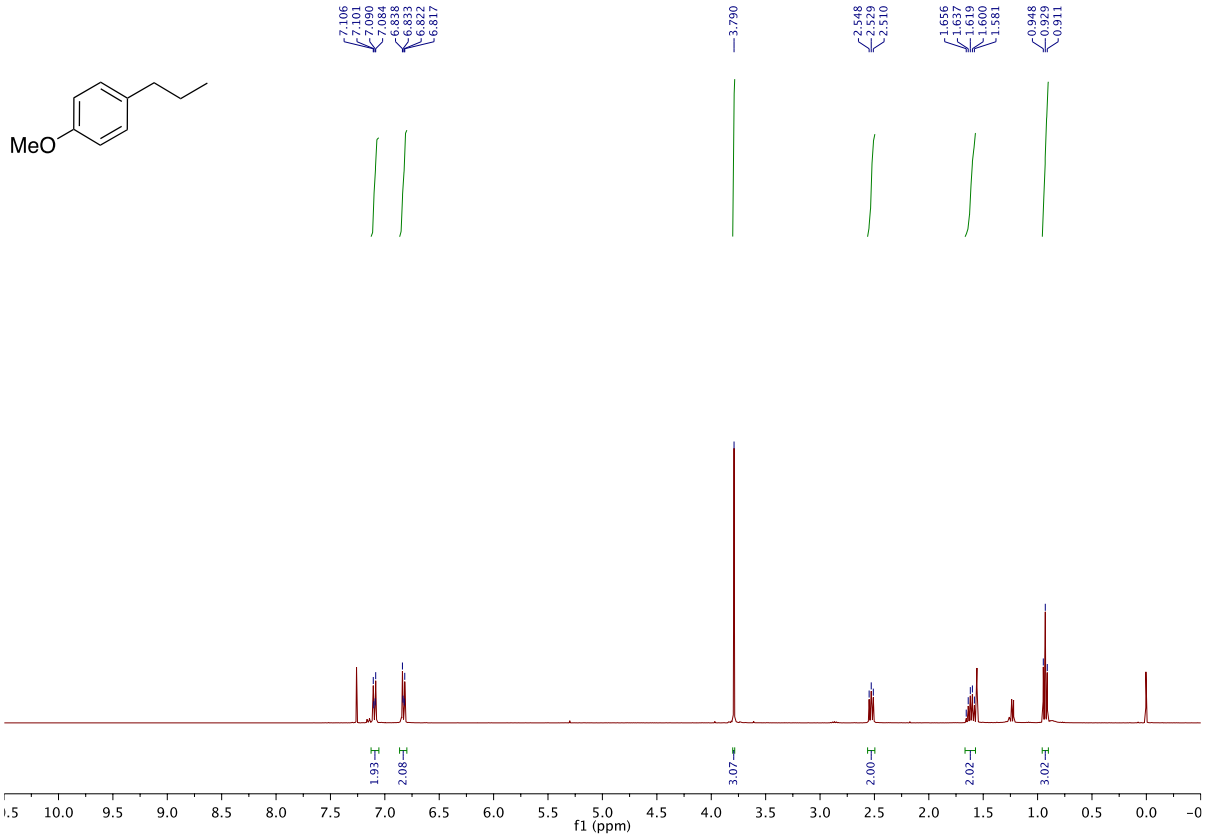
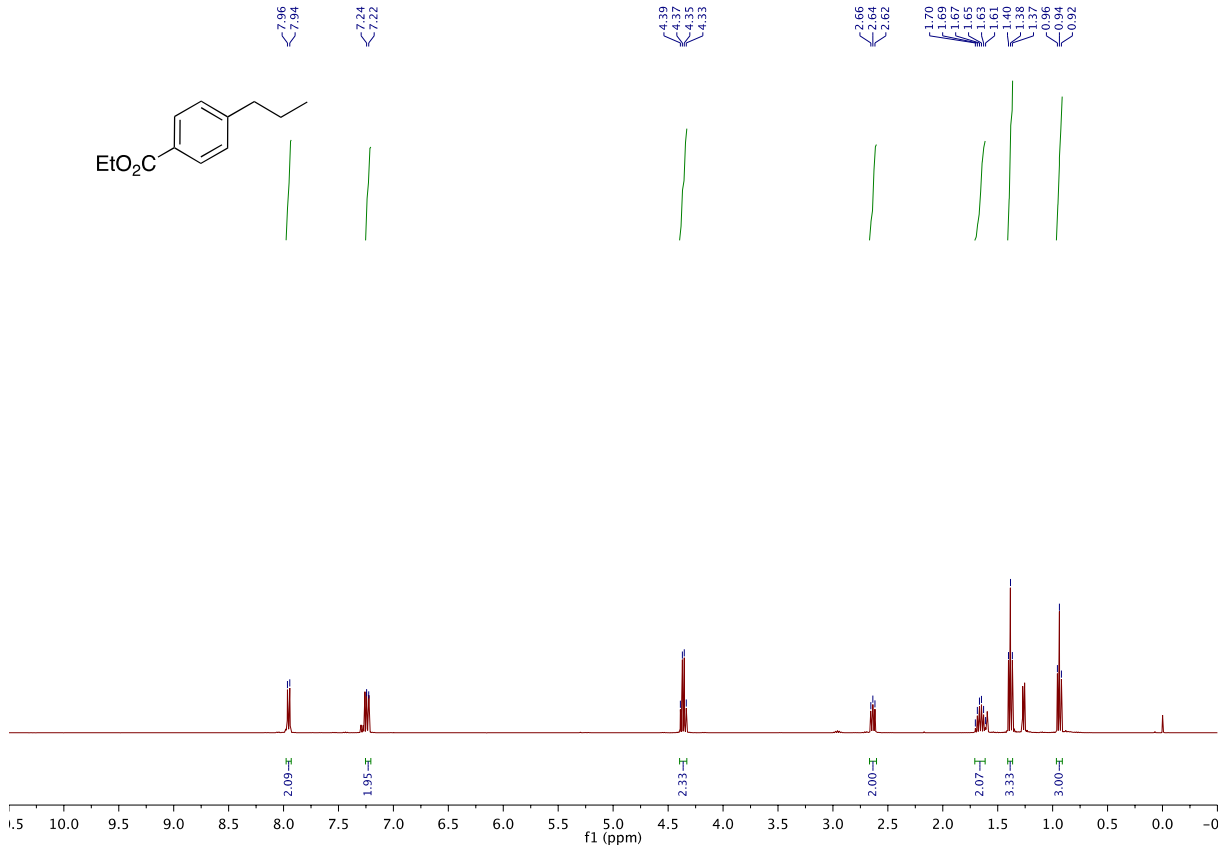


Ethyl 4-propylbenzoate



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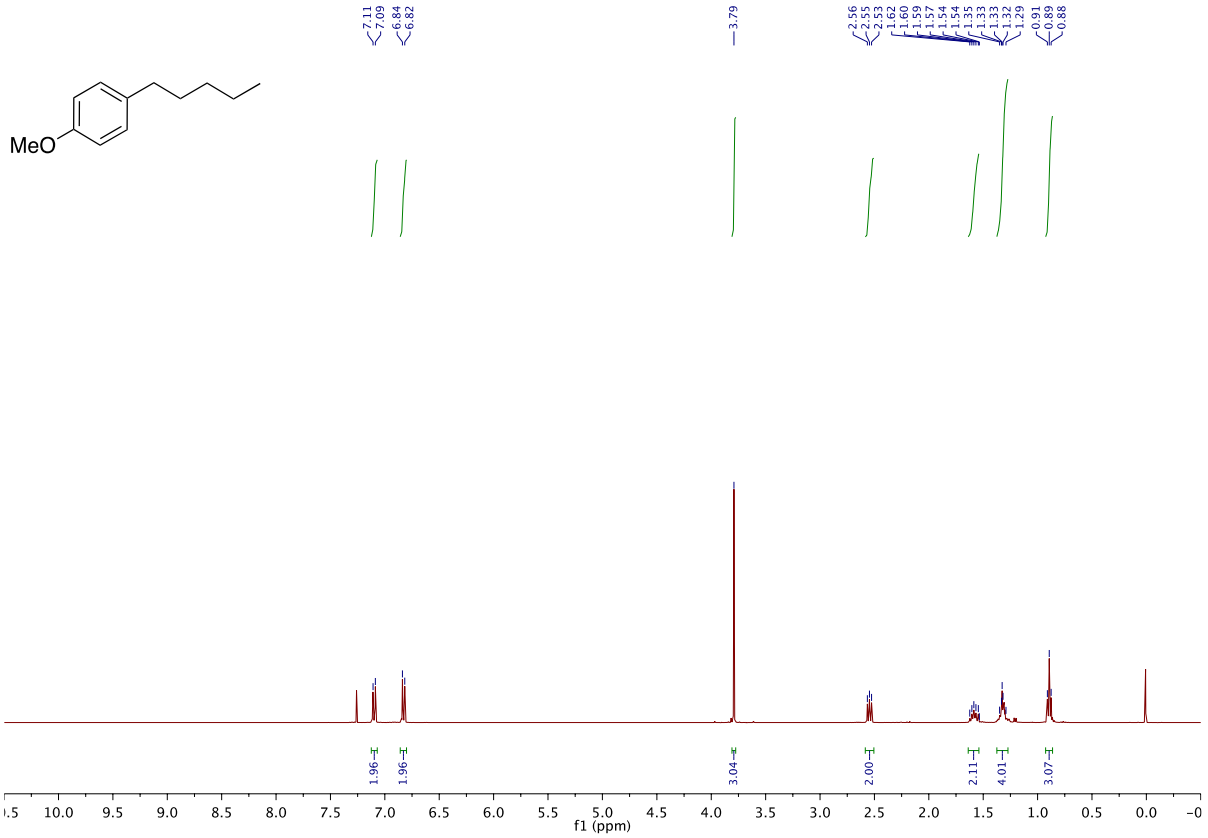
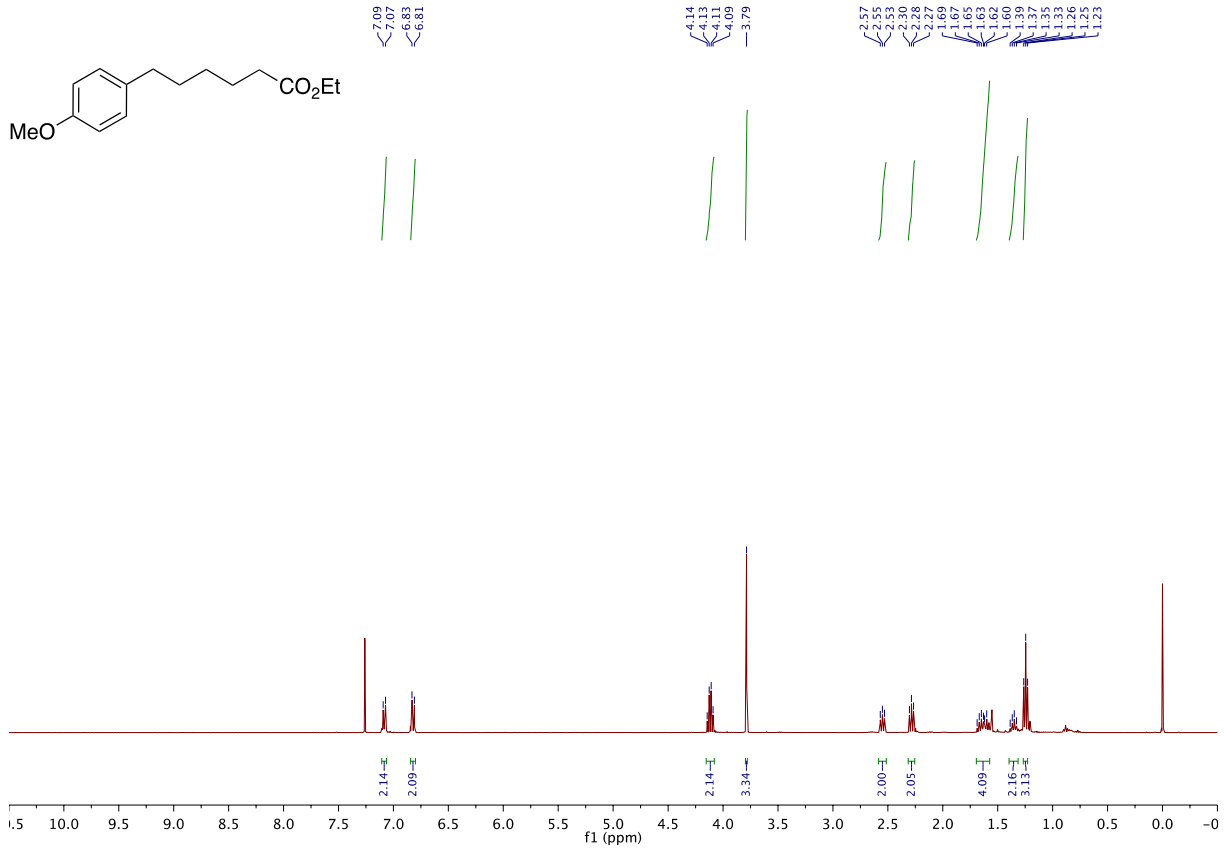


Ethyl 6-(4-methoxyphenyl)hexanoate



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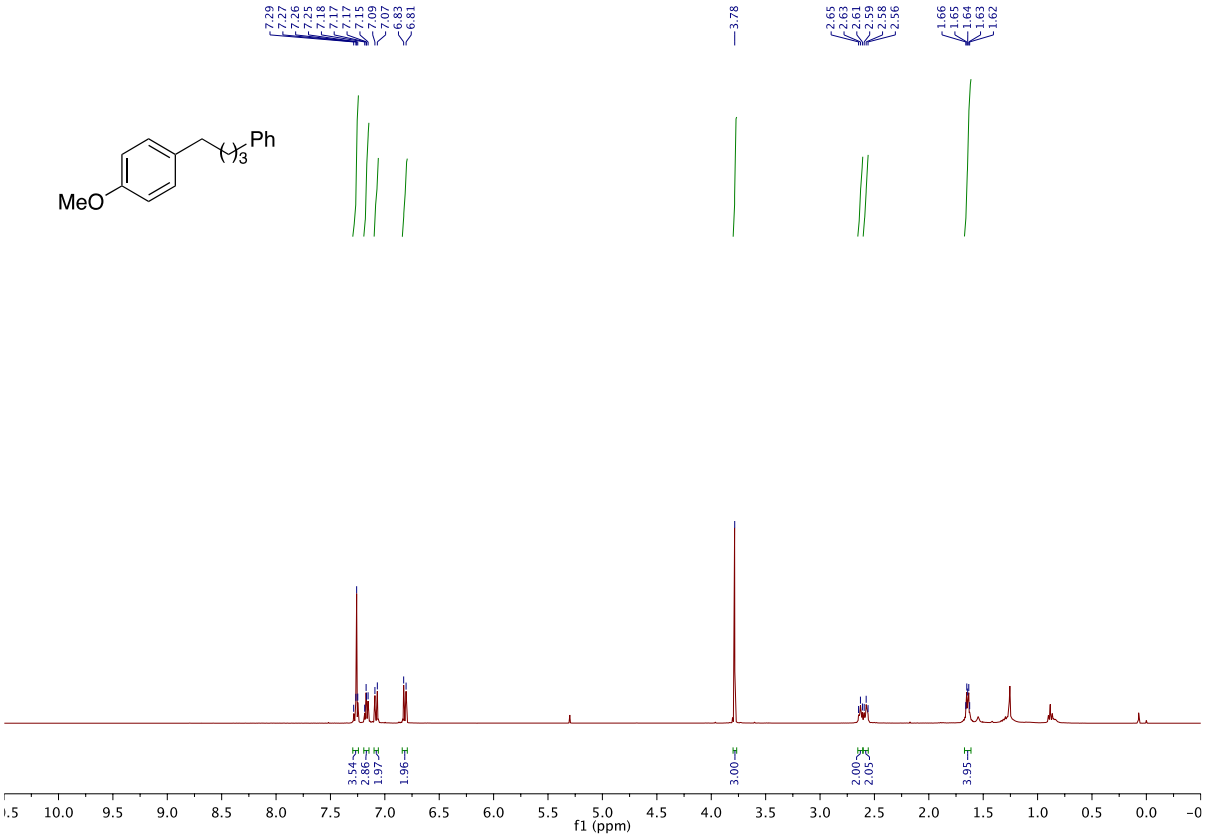

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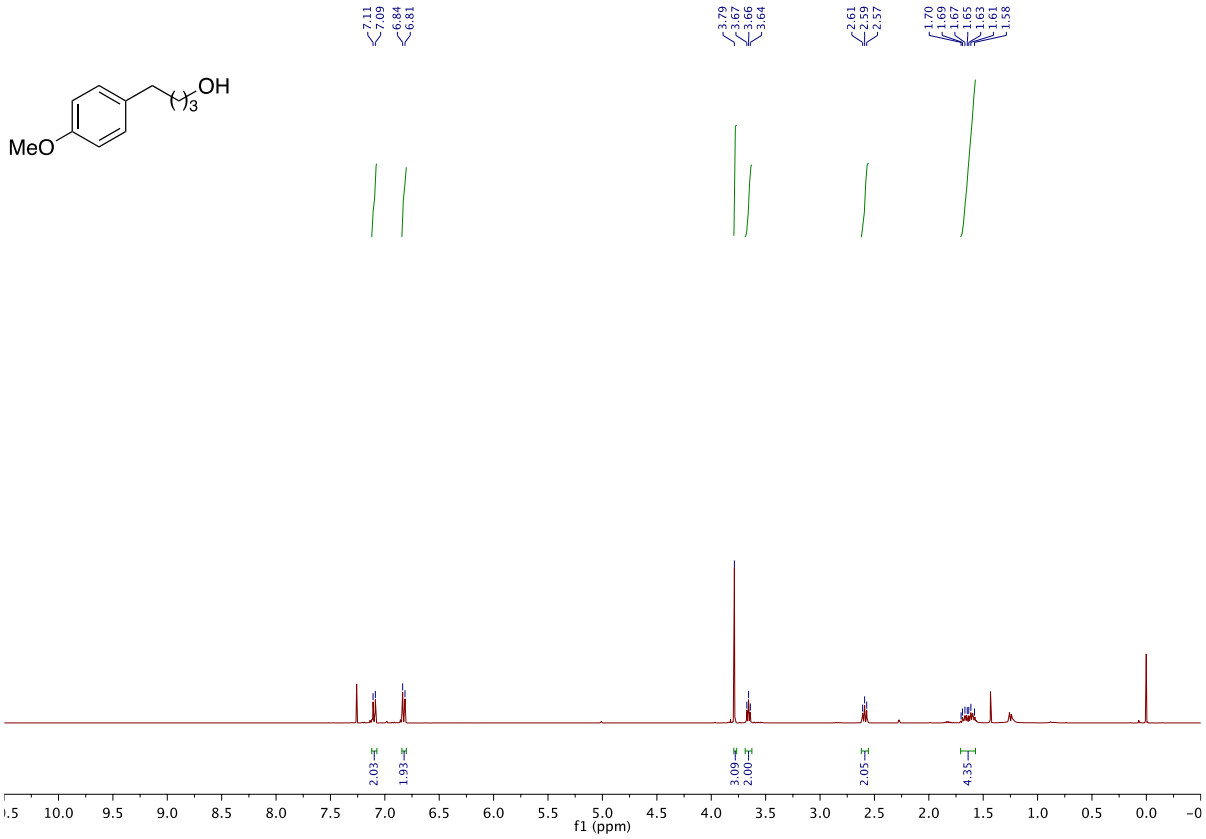

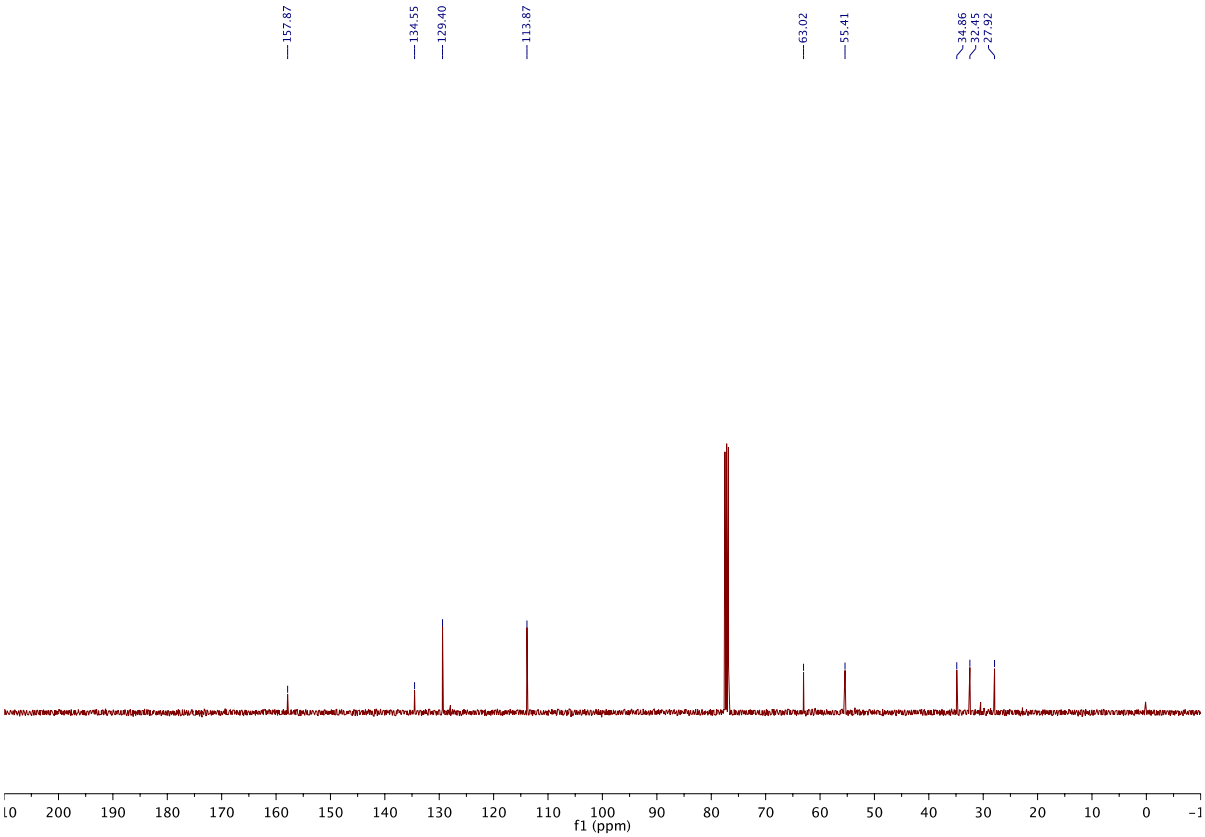

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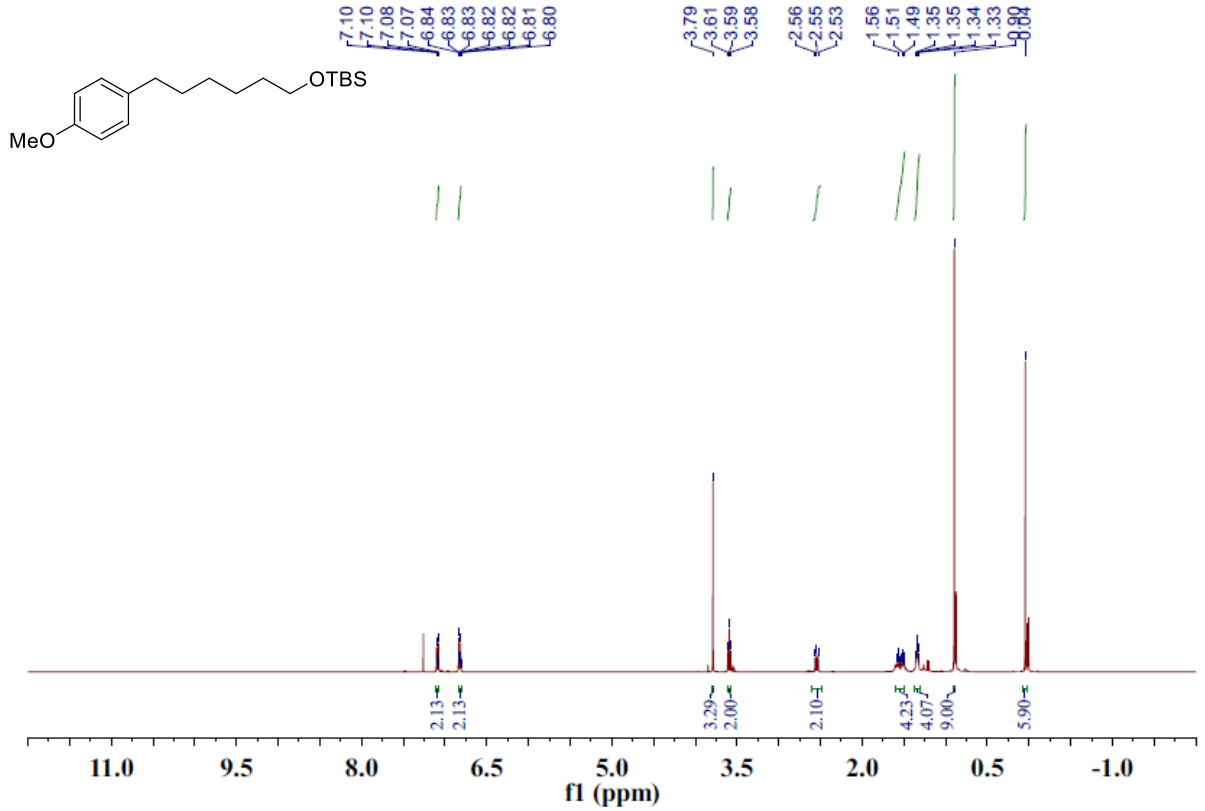
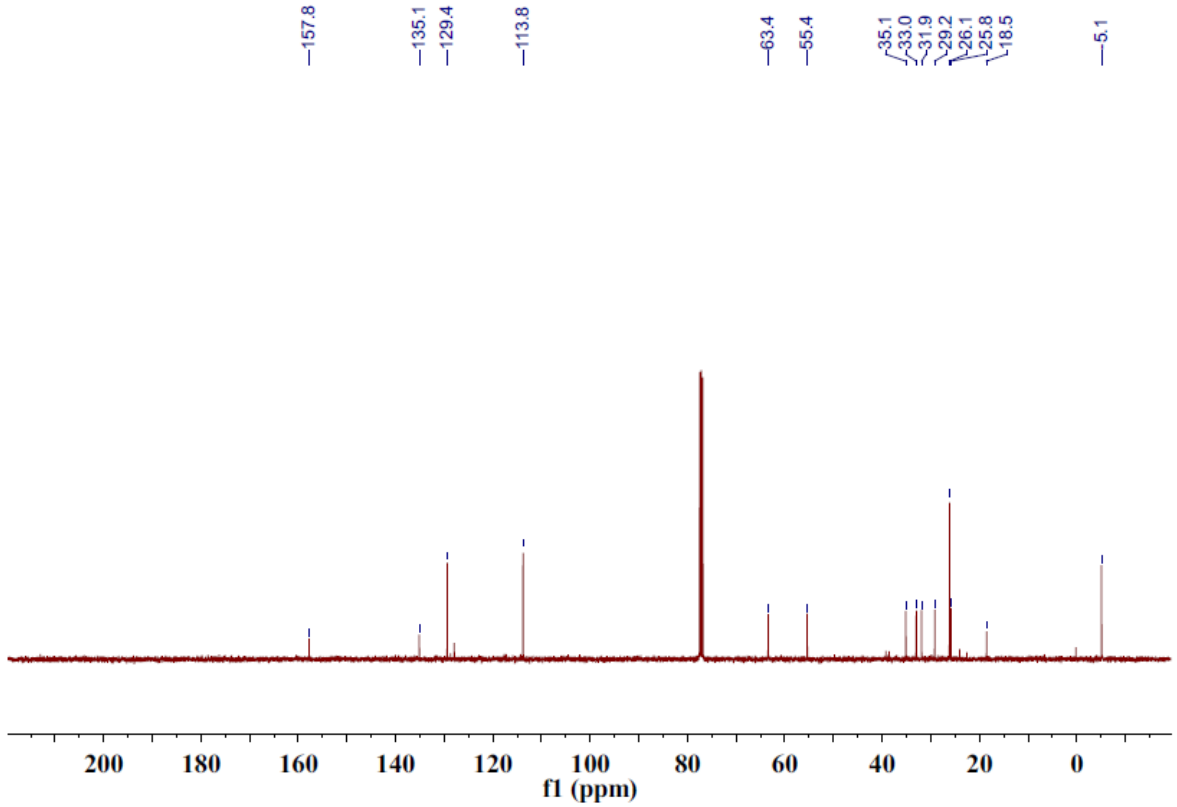
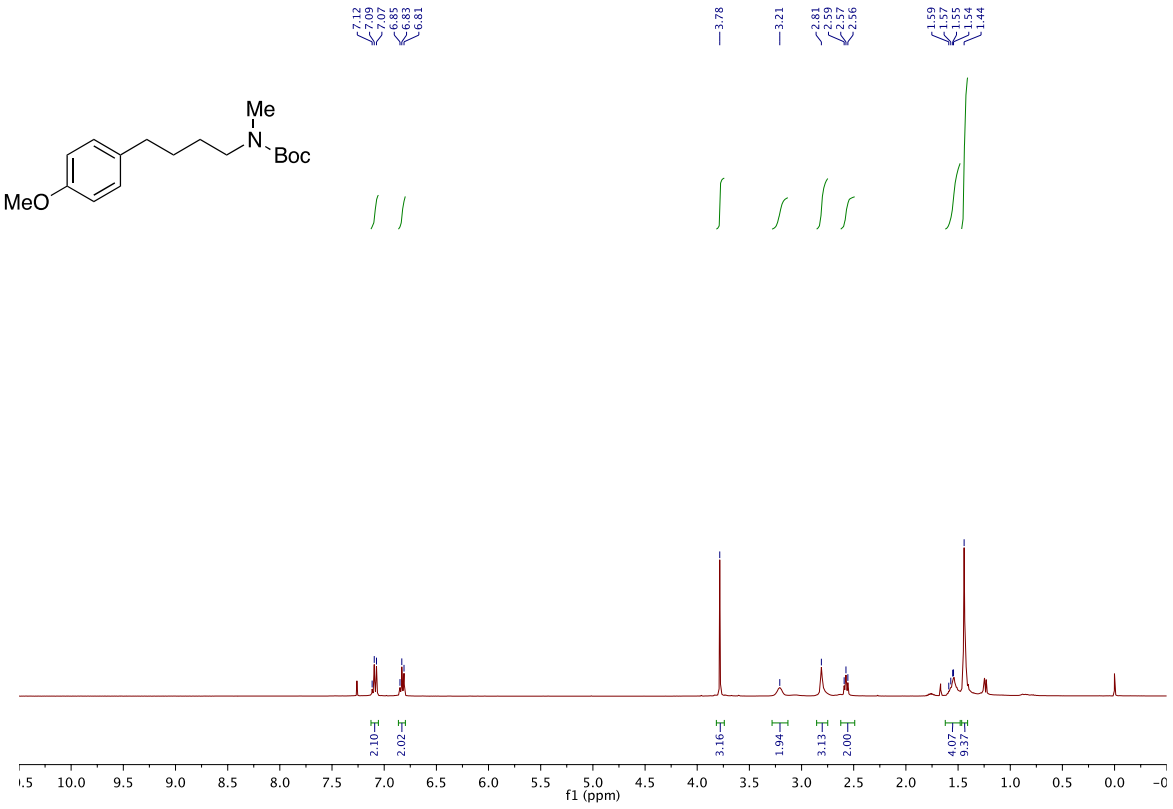
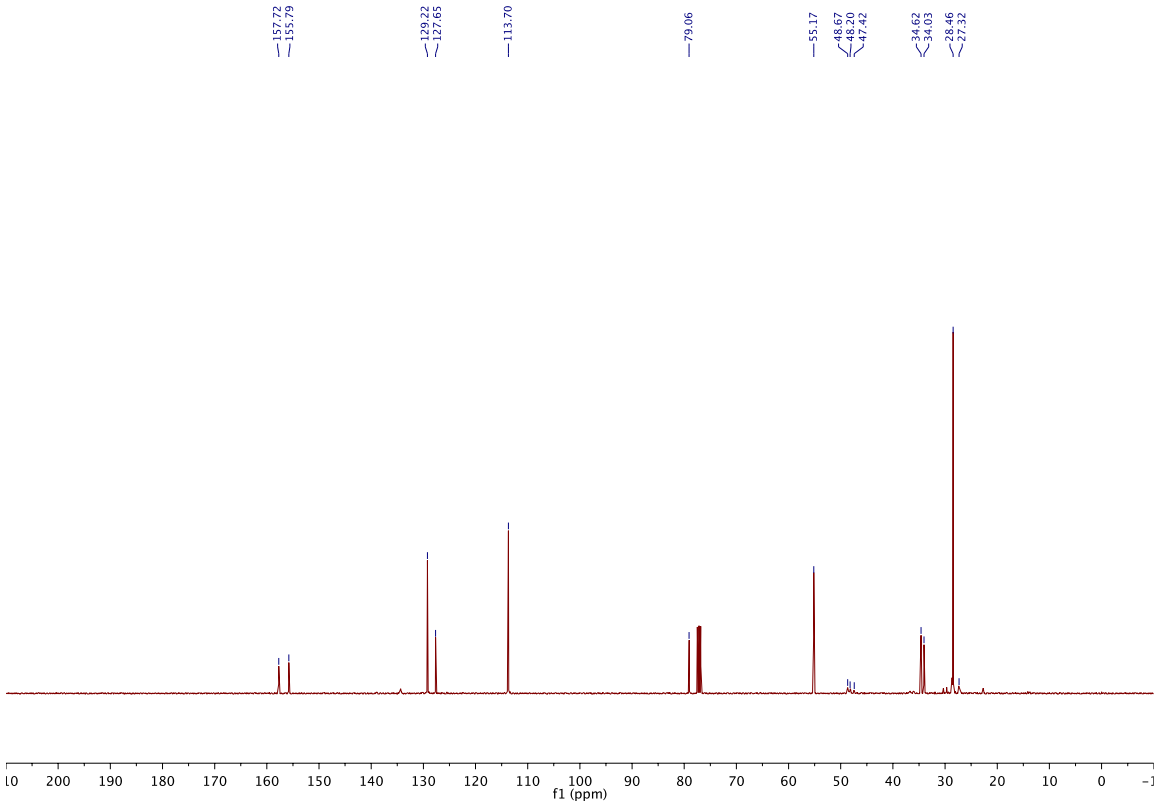


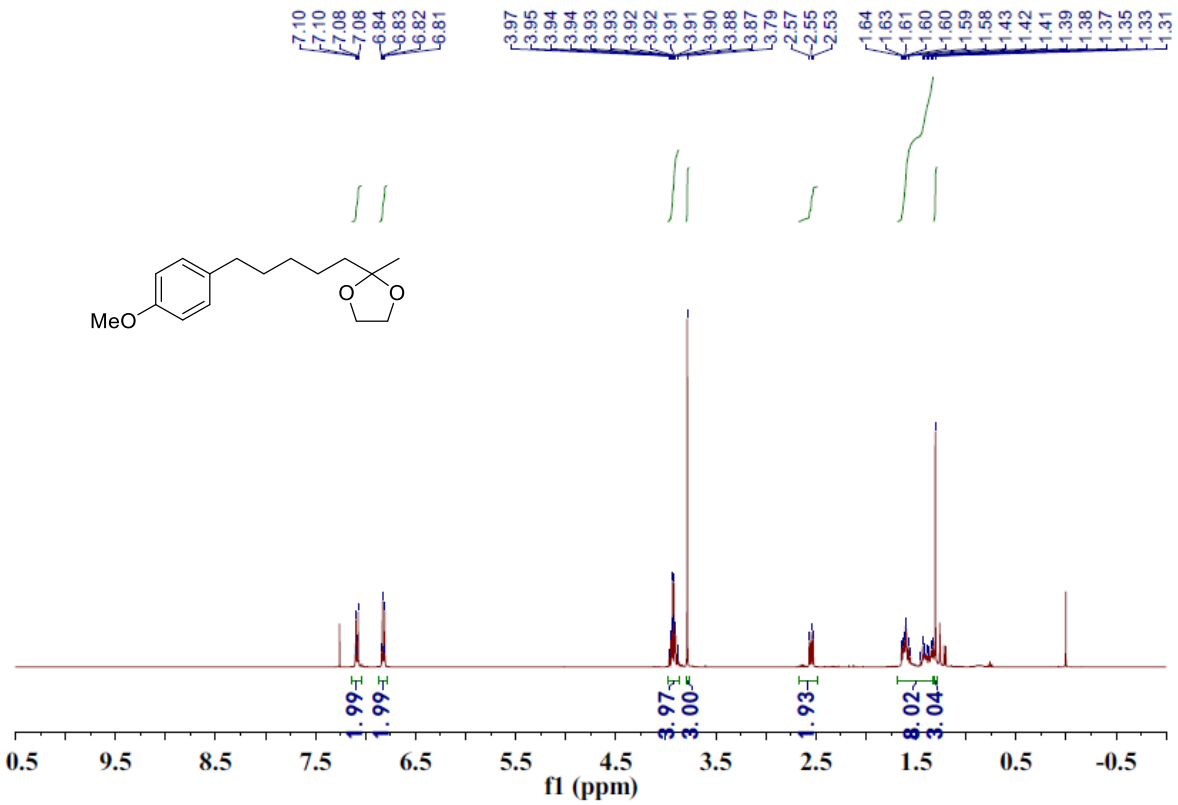


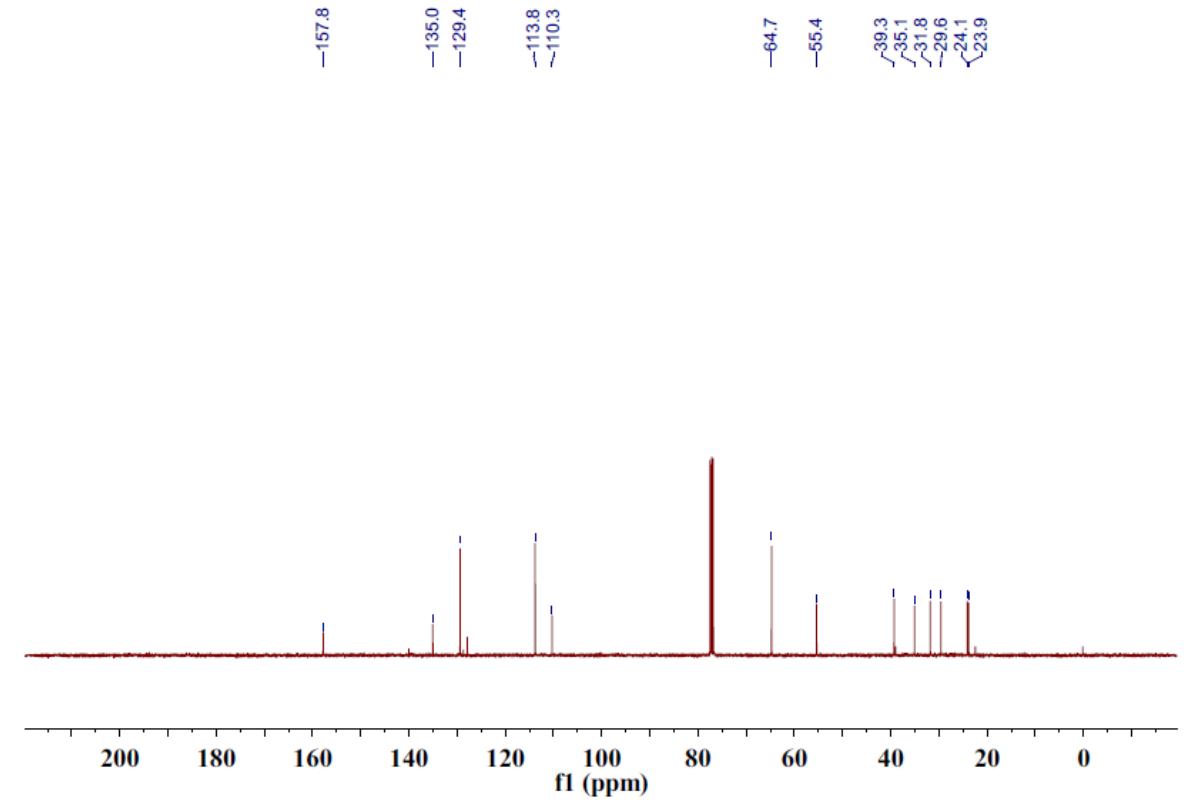
***tert*-Butyl (4-(4-methoxyphenyl)butyl)(methyl)carbamate**



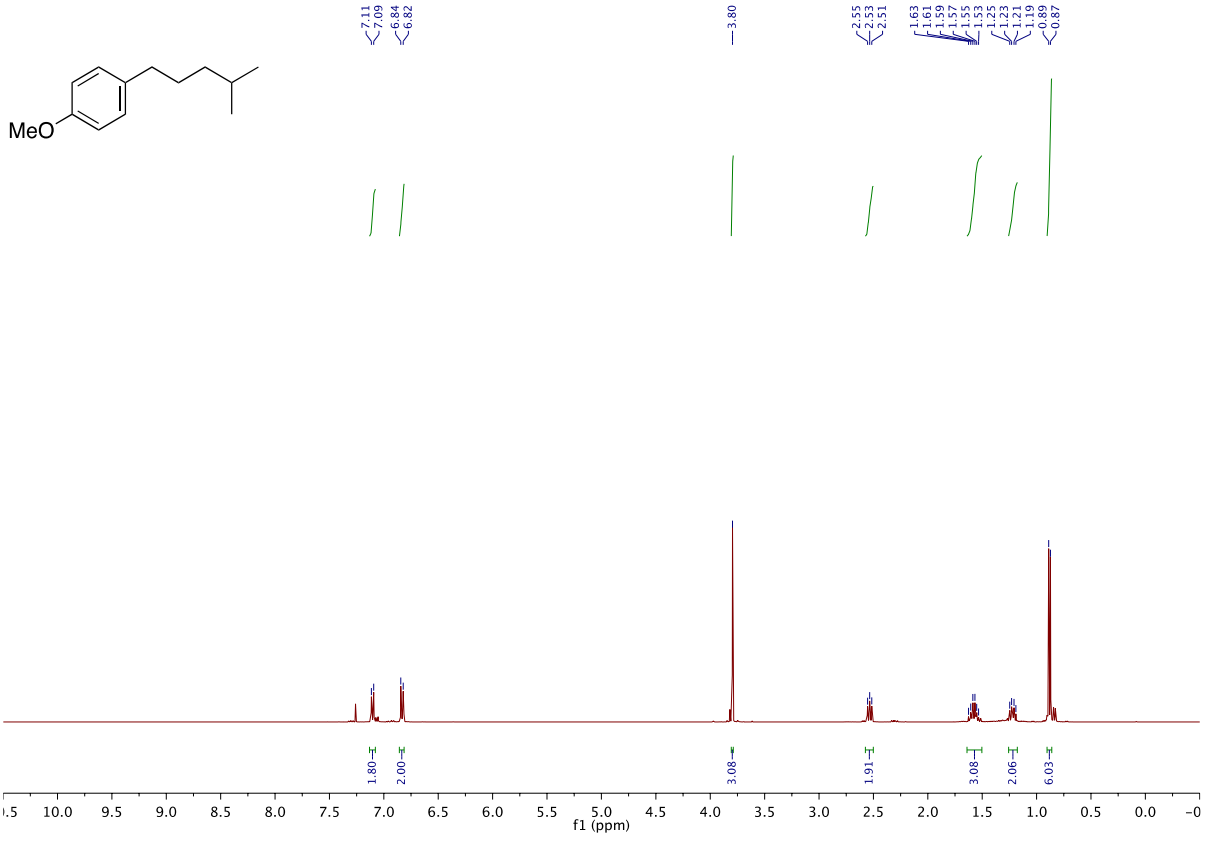


2-(5-(4-methoxyphenyl)pentyl)-2-methyl-1,3-dioxolane

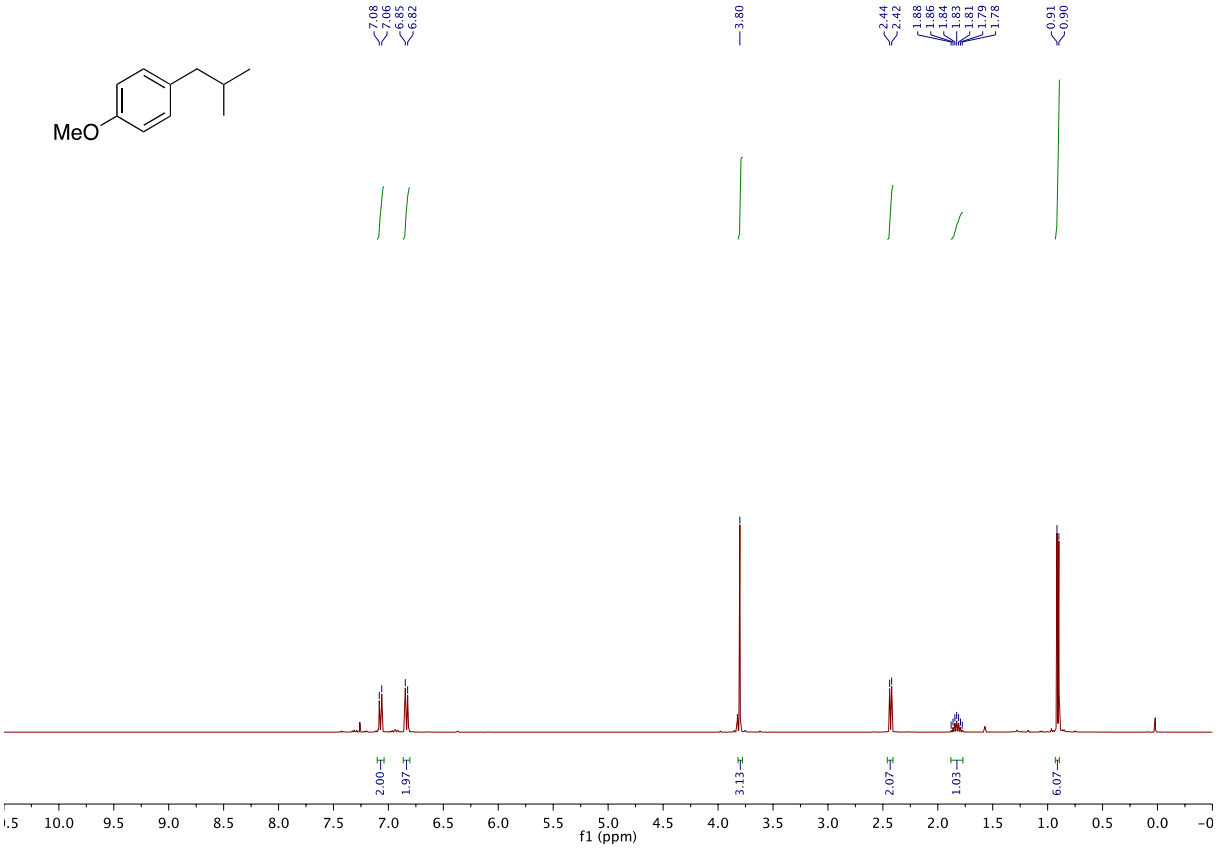




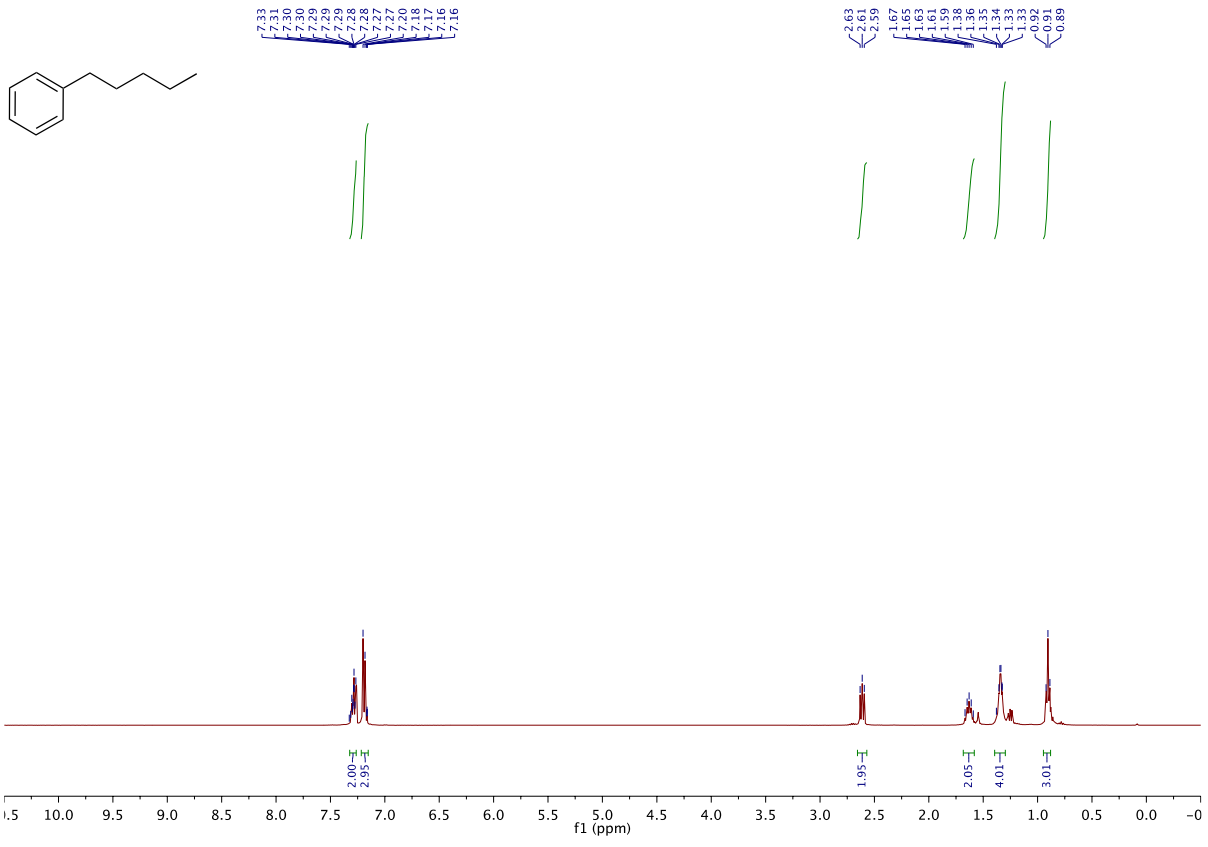
1-Methoxy-4-(4-methylpentyl)benzene



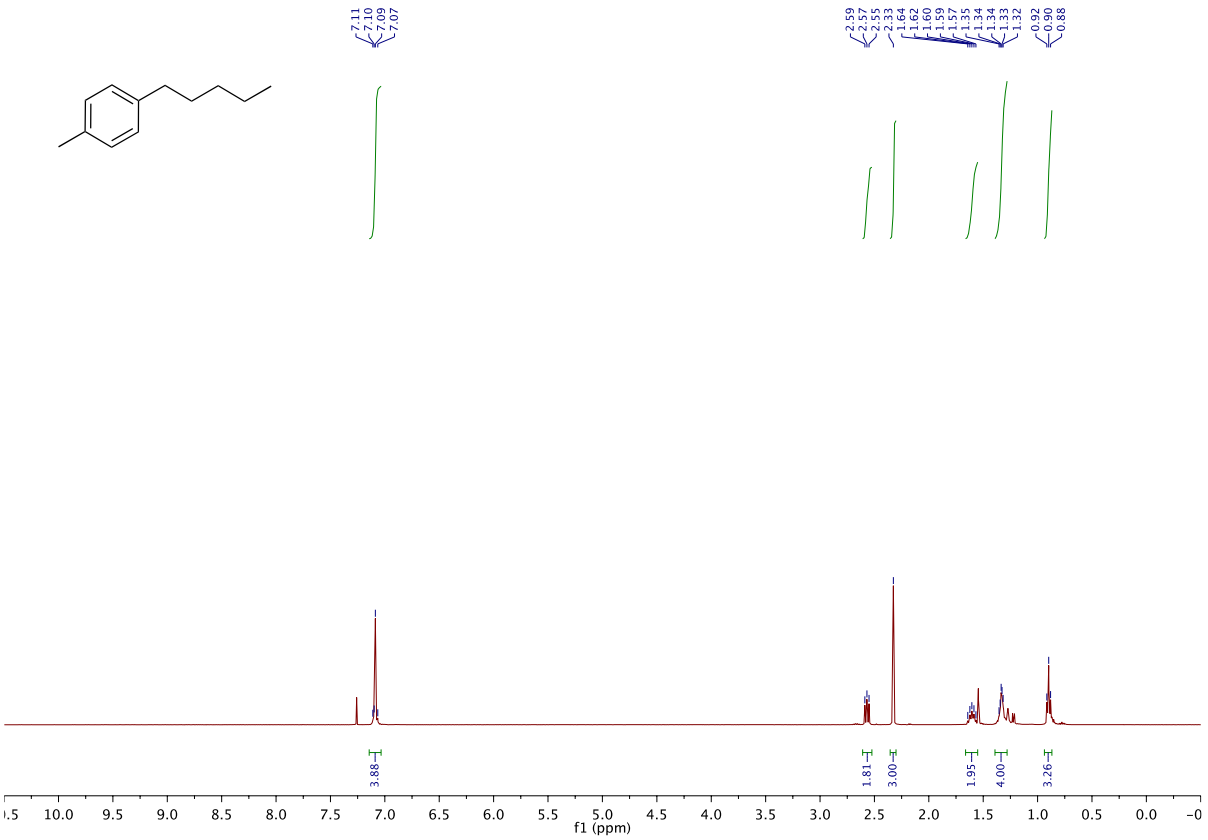
1-Isobutyl-4-methoxybenzene



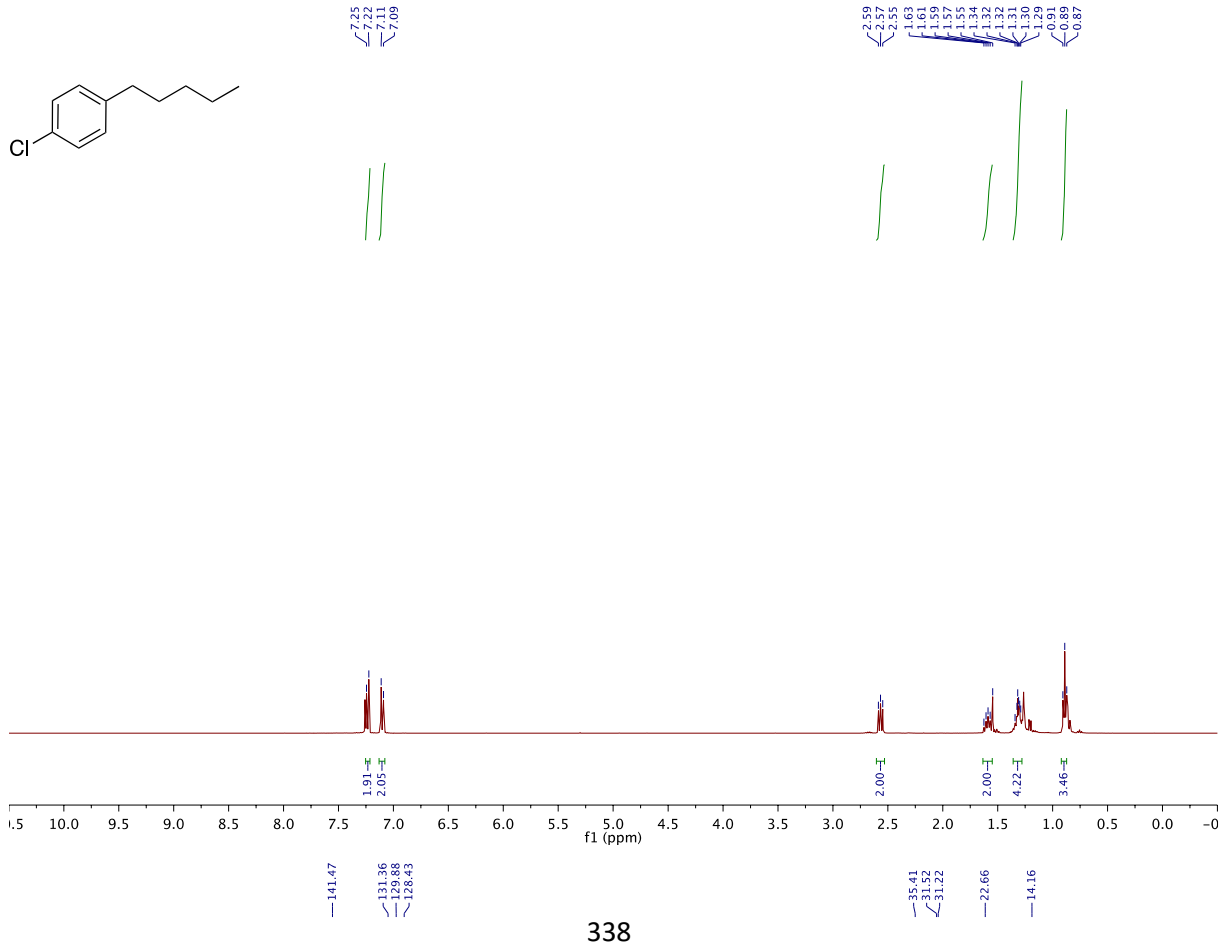
Pentylbenzene



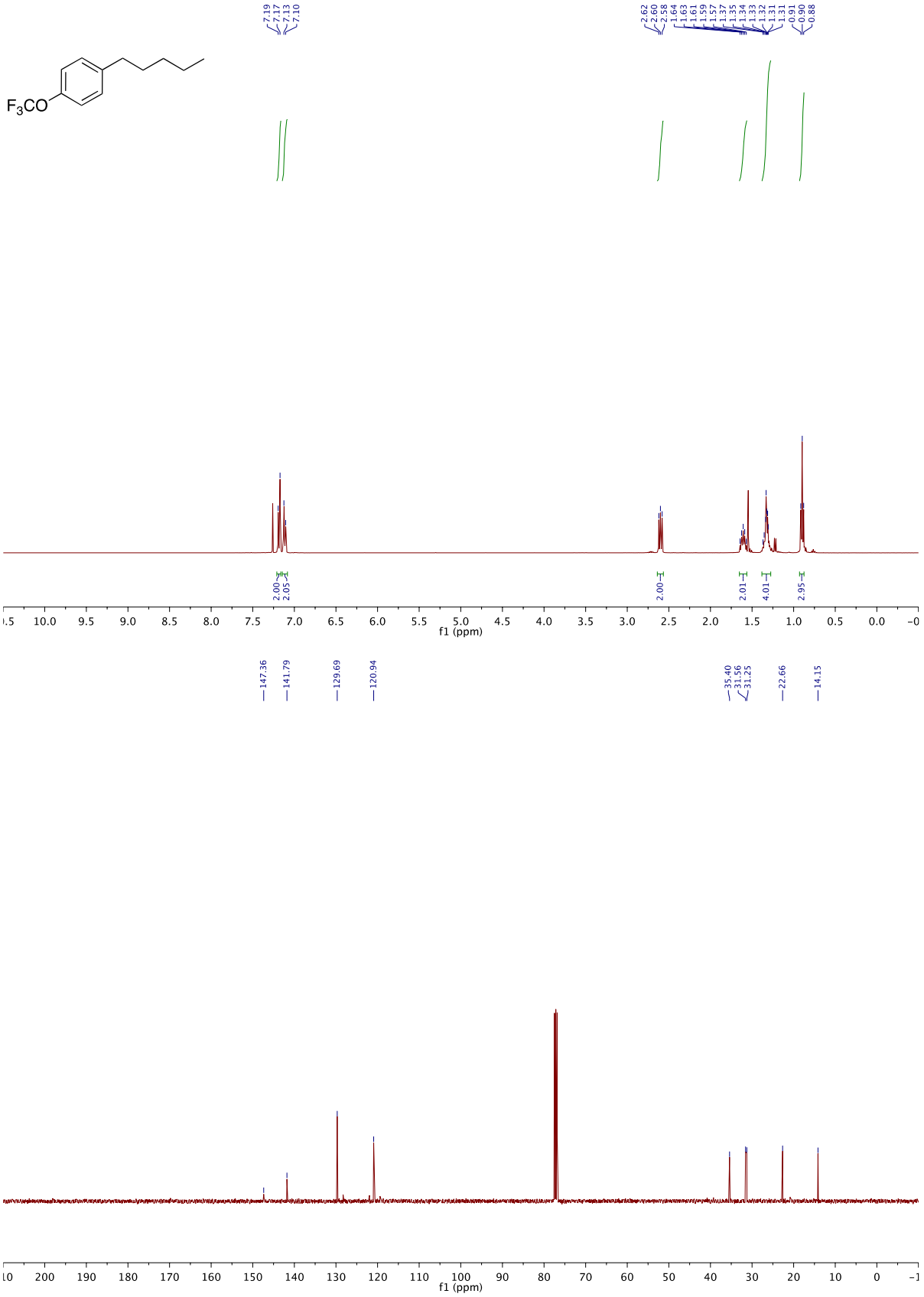
1-Methyl-4-pentylbenzene

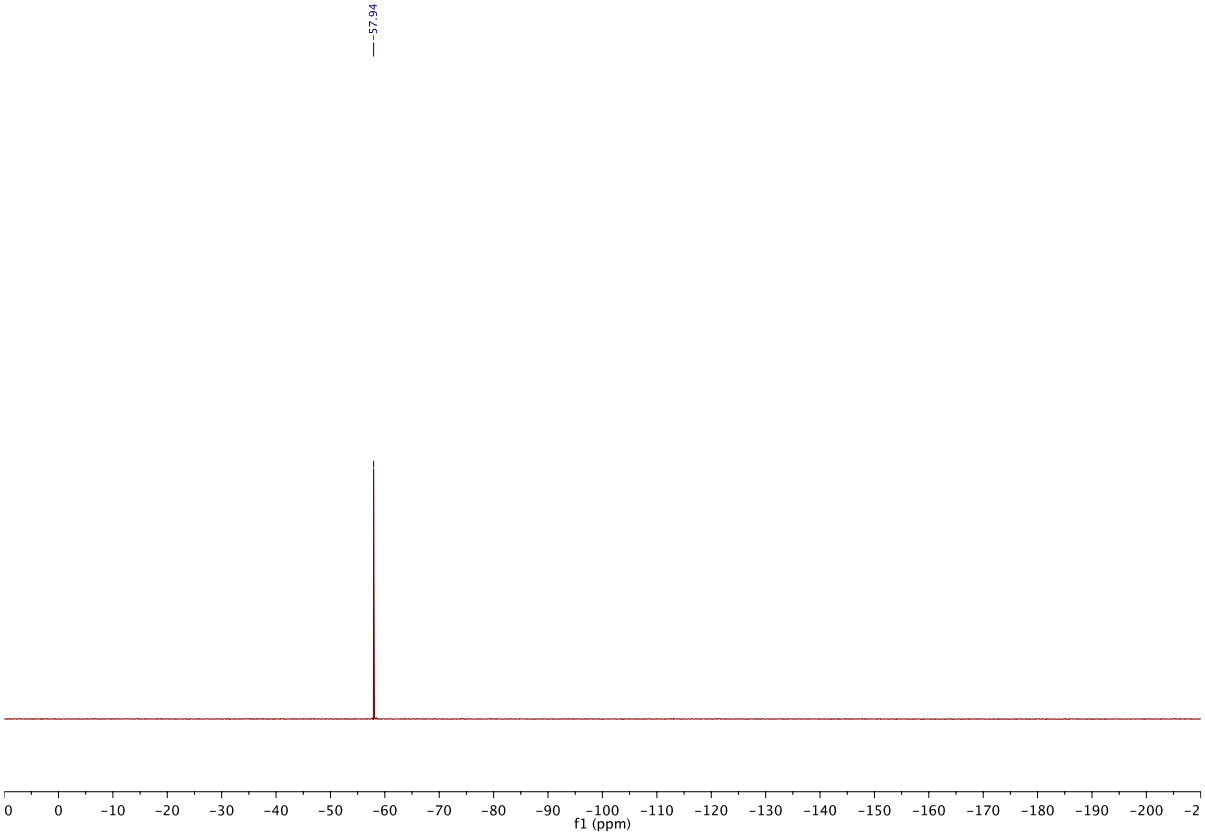


1-Chloro-4-pentylbenzene

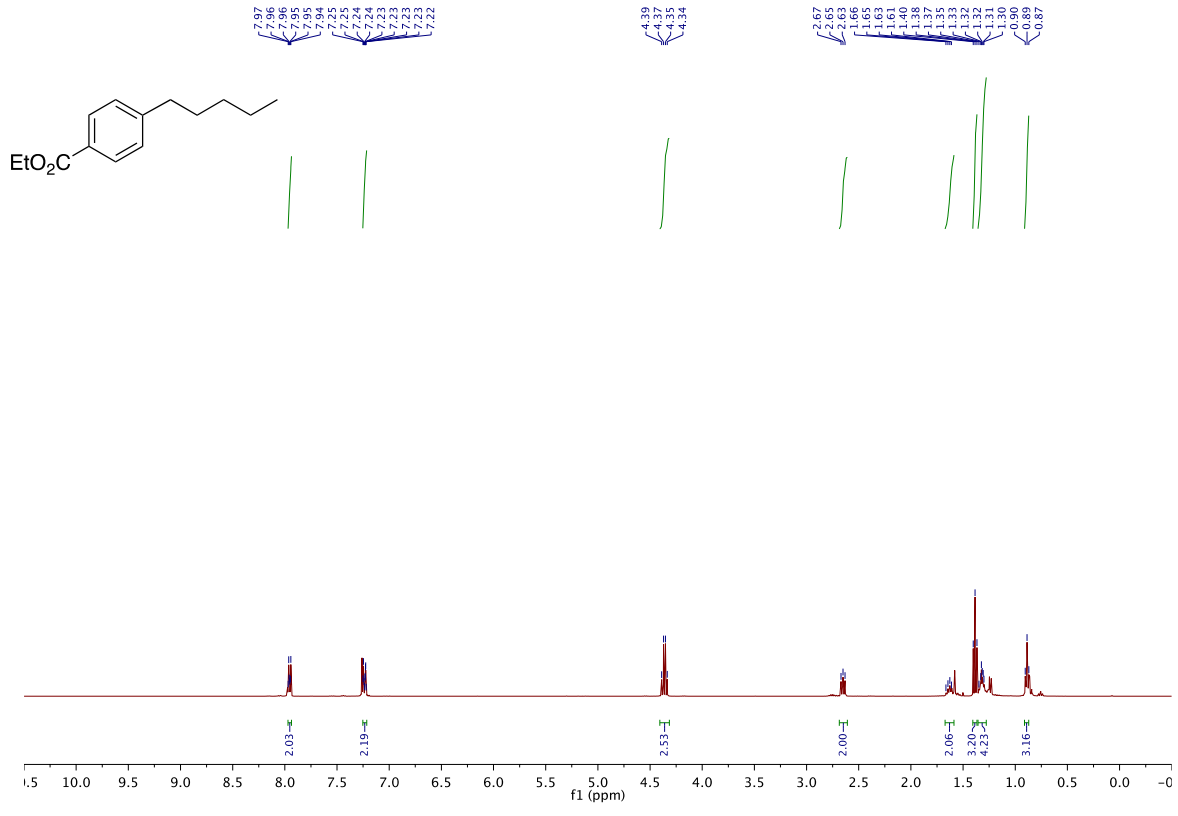


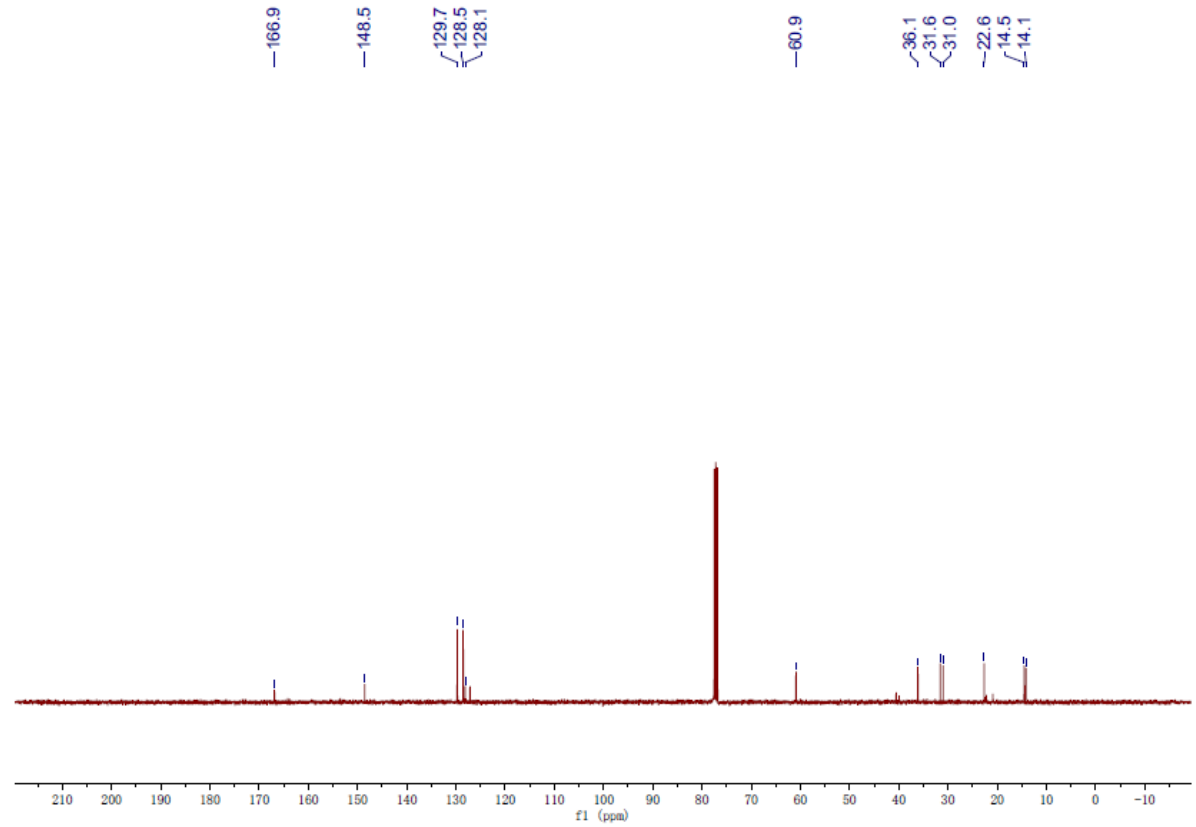
1-Pentyl-4-(trifluoromethoxy)benzene



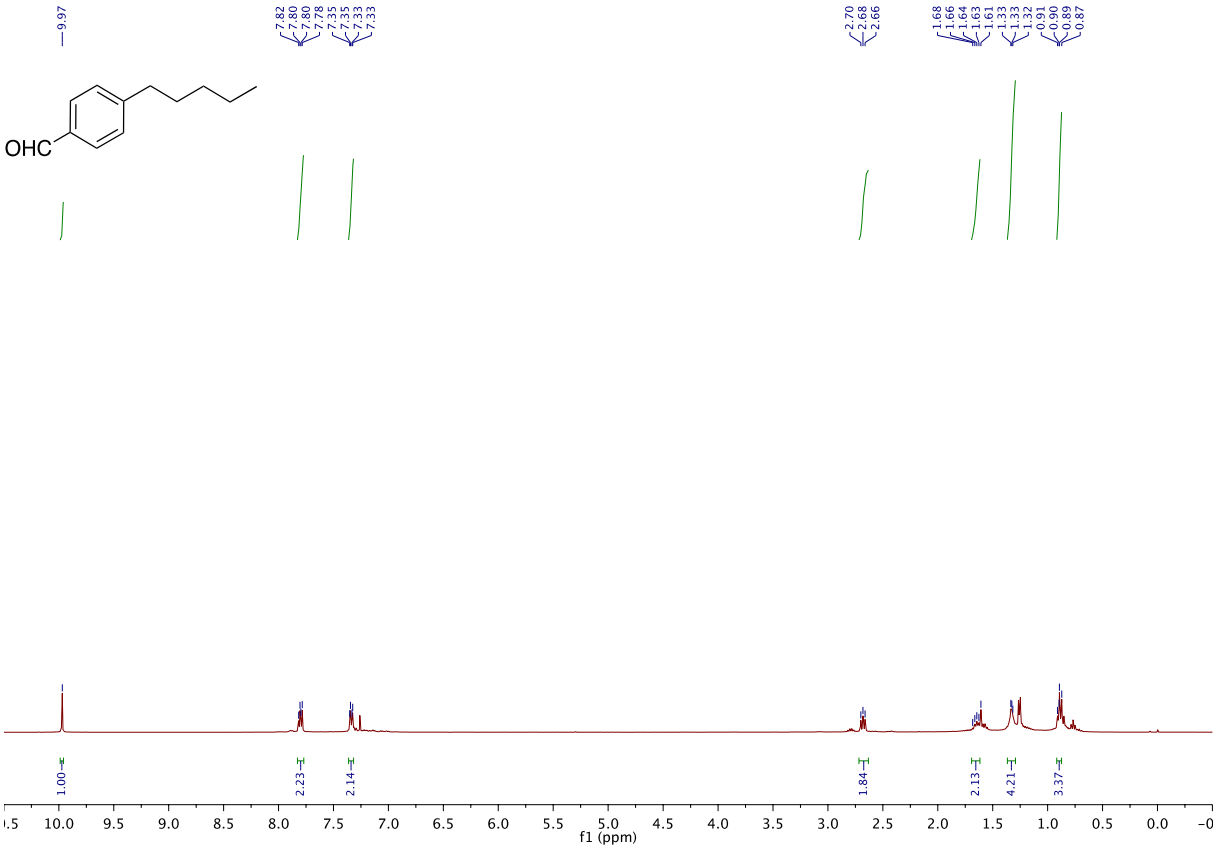


Ethyl 4-pentylbenzoate

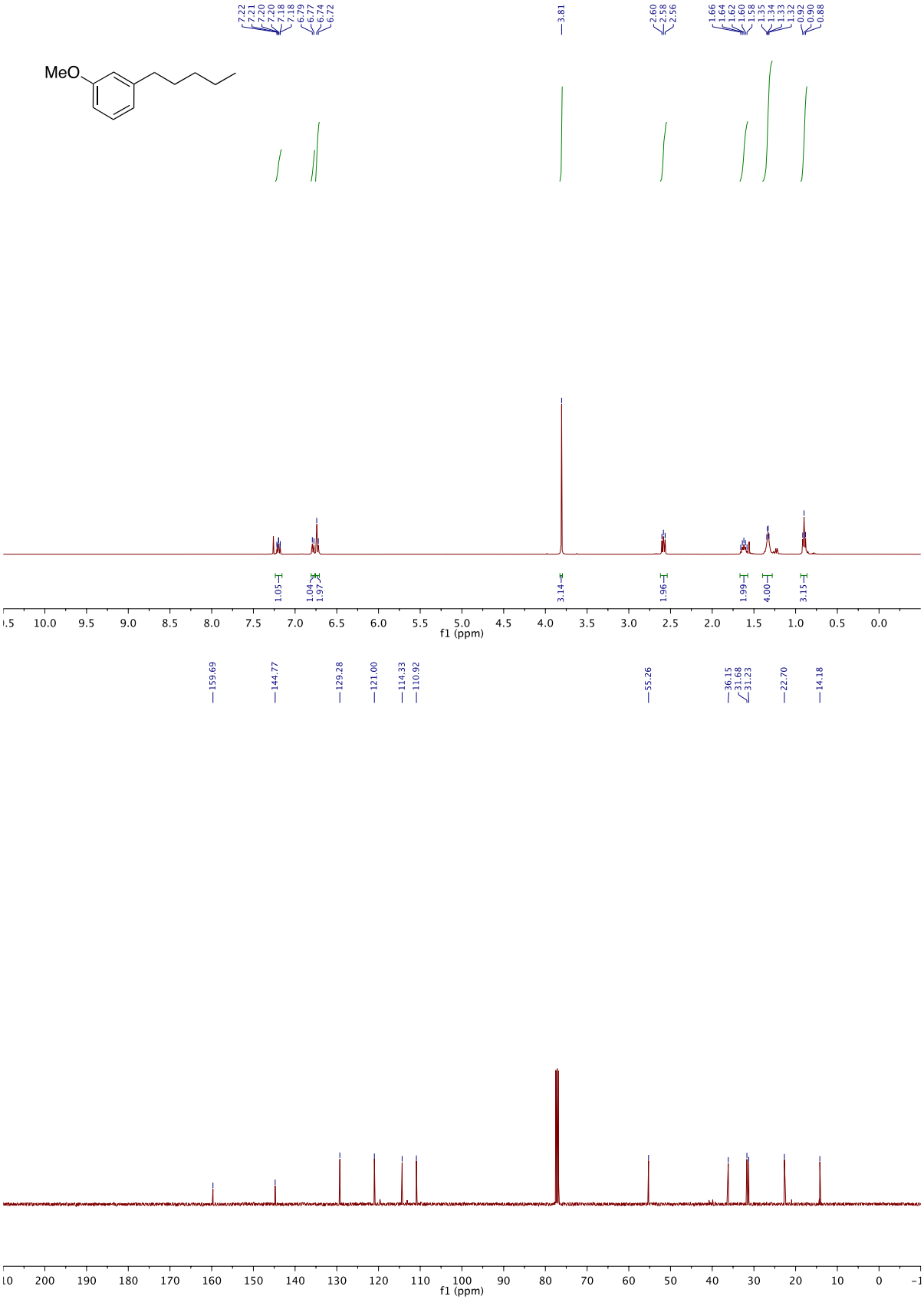




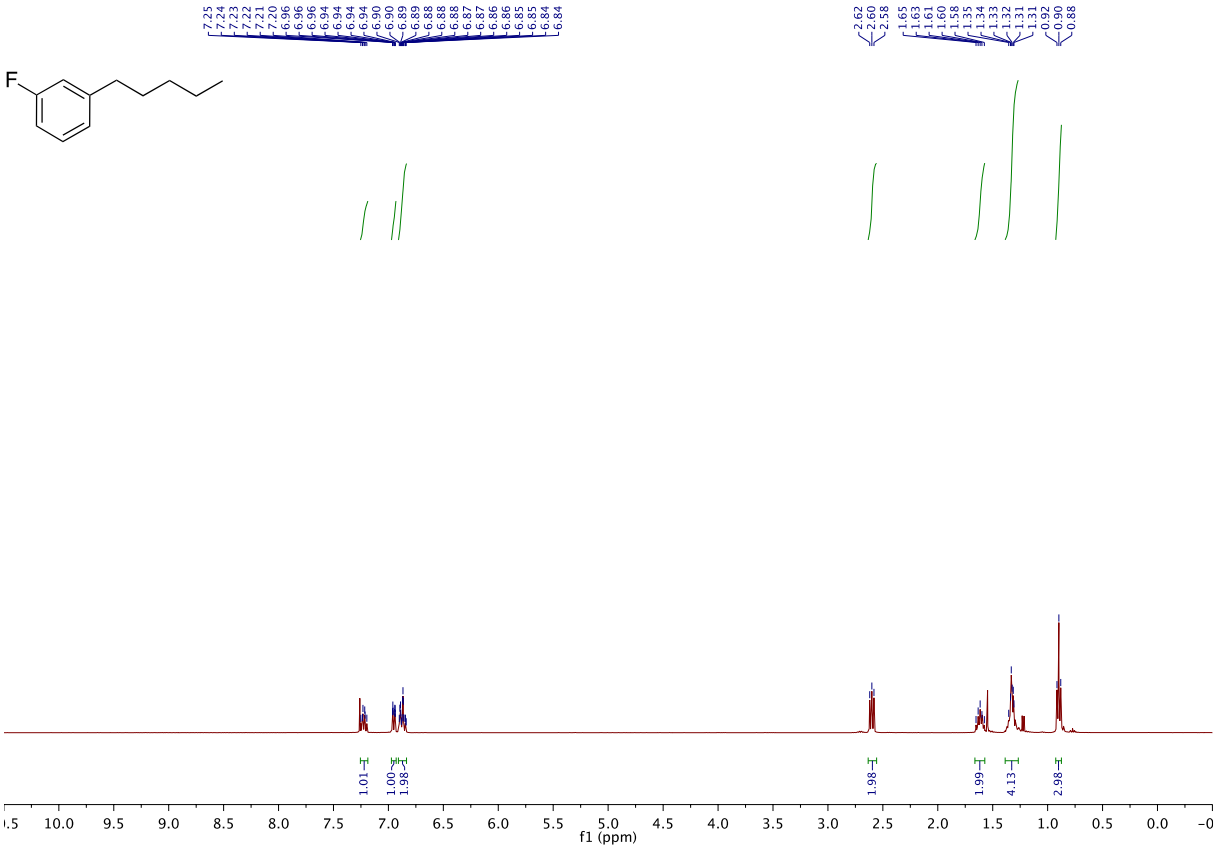
4-Pentylbenzaldehyde

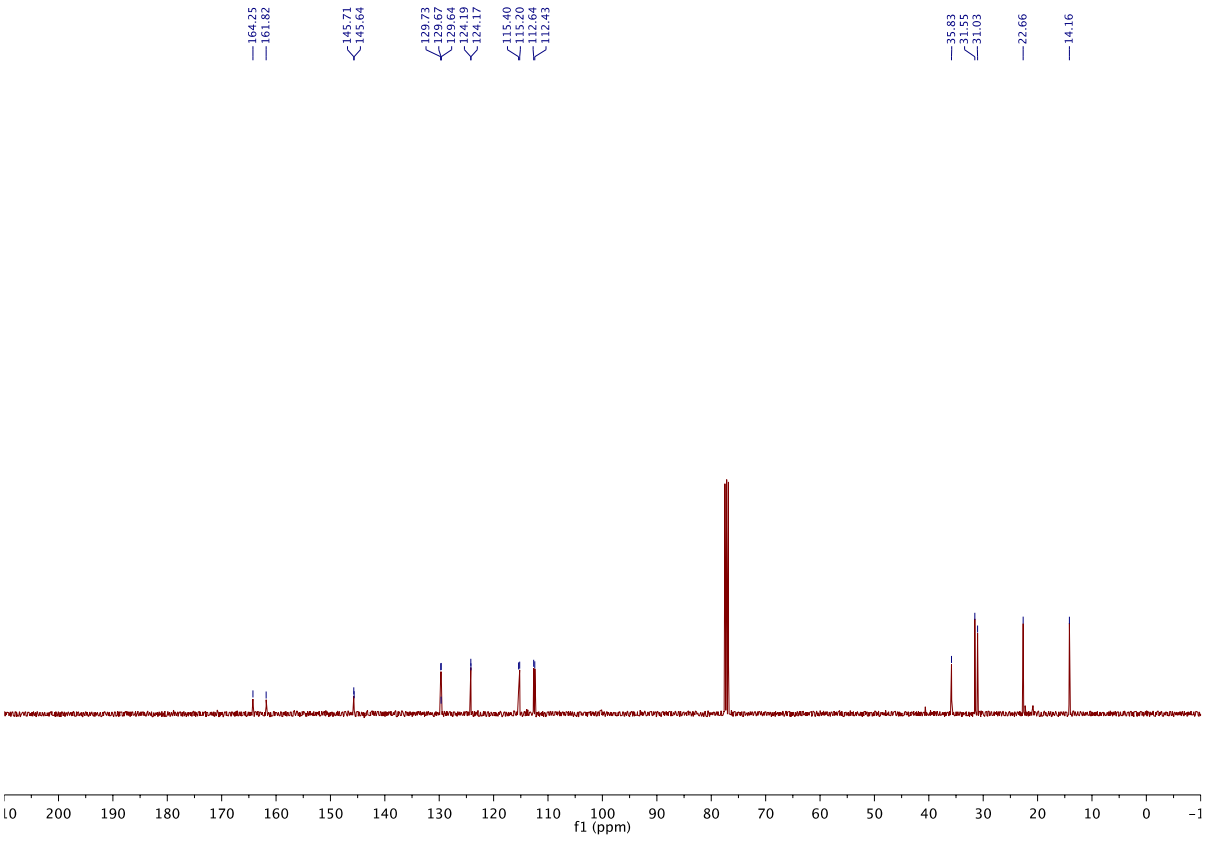


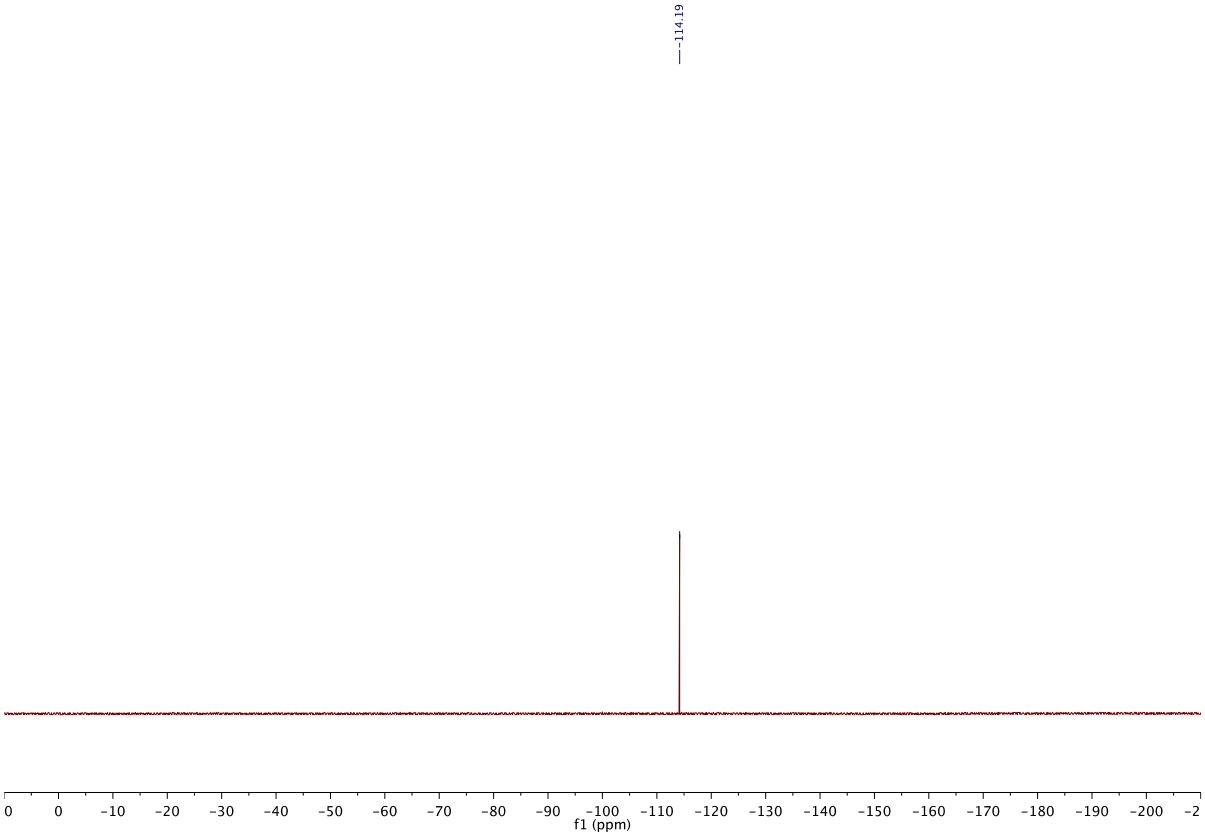
1-Methoxy-3-pentylbenzene



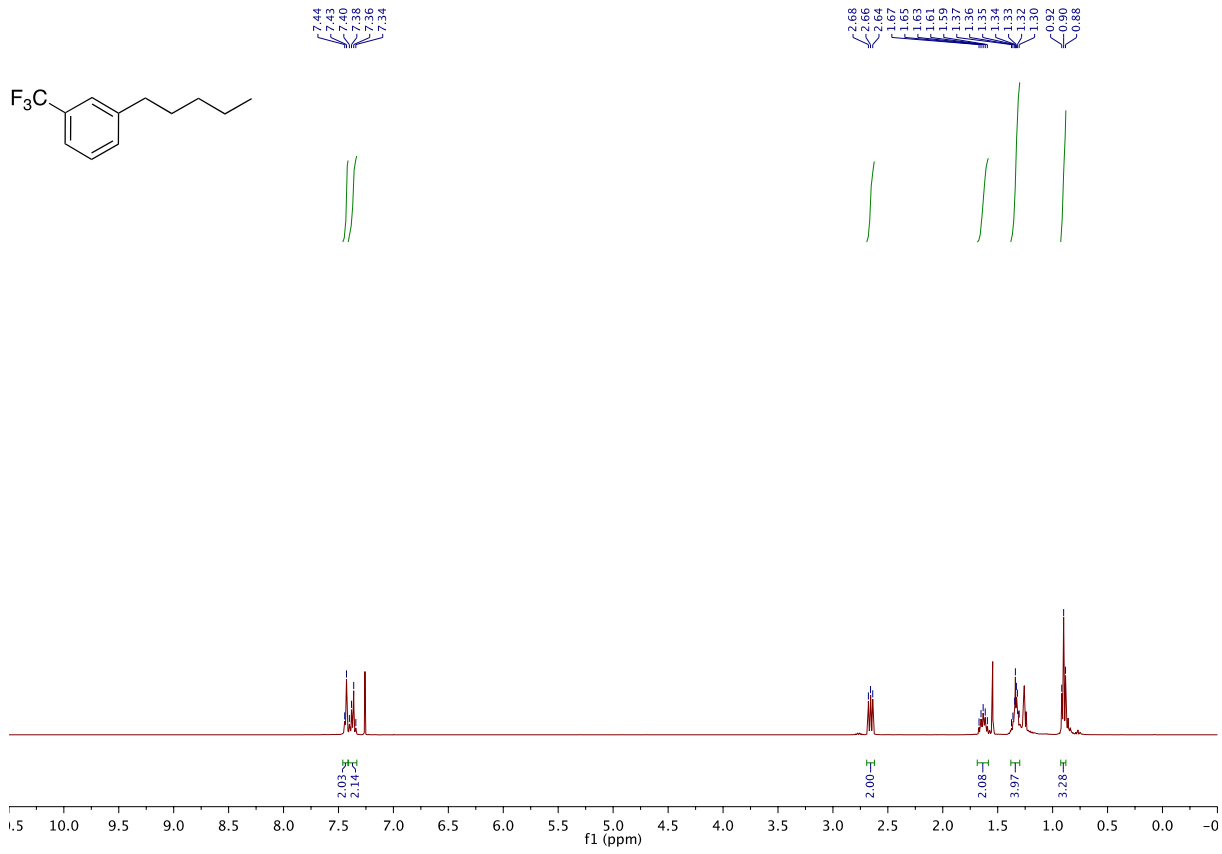
1-Fluoro-3-pentylbenzene

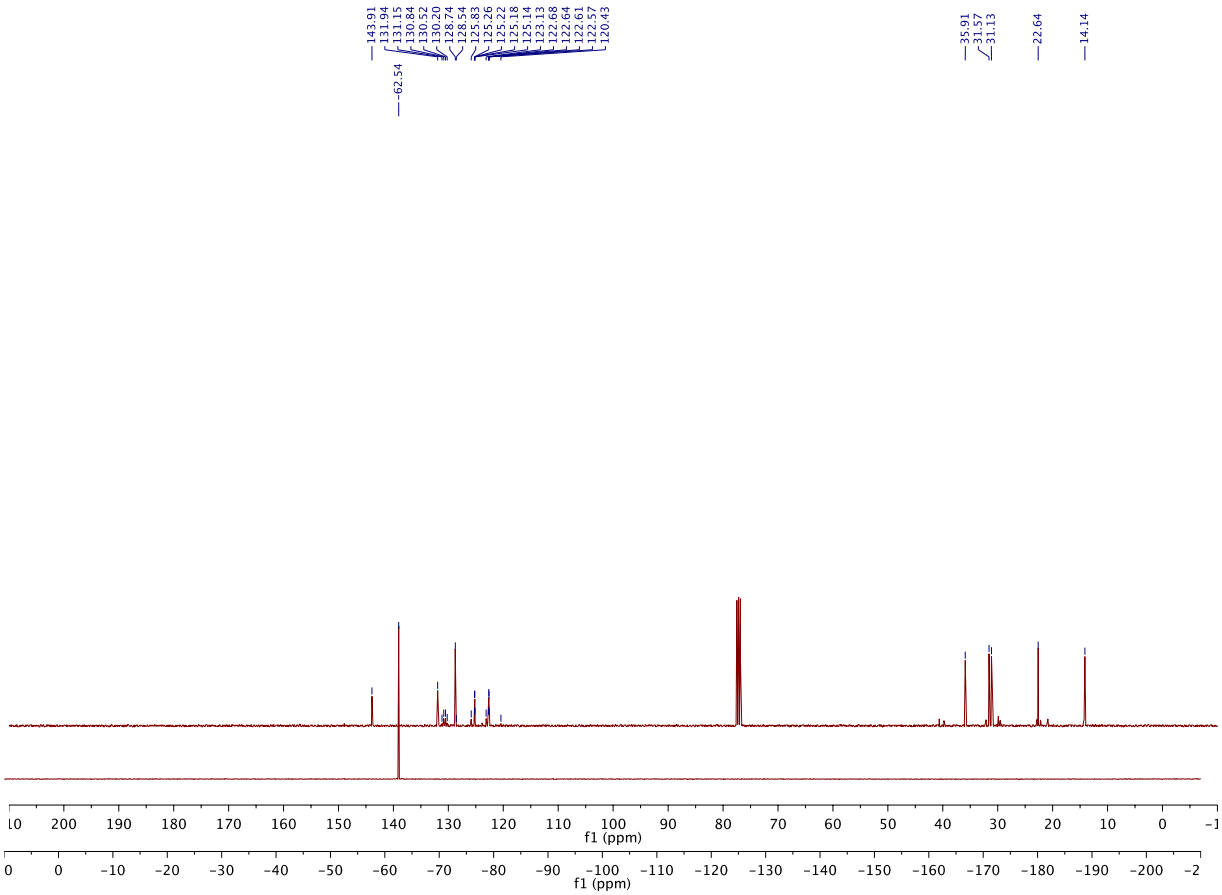




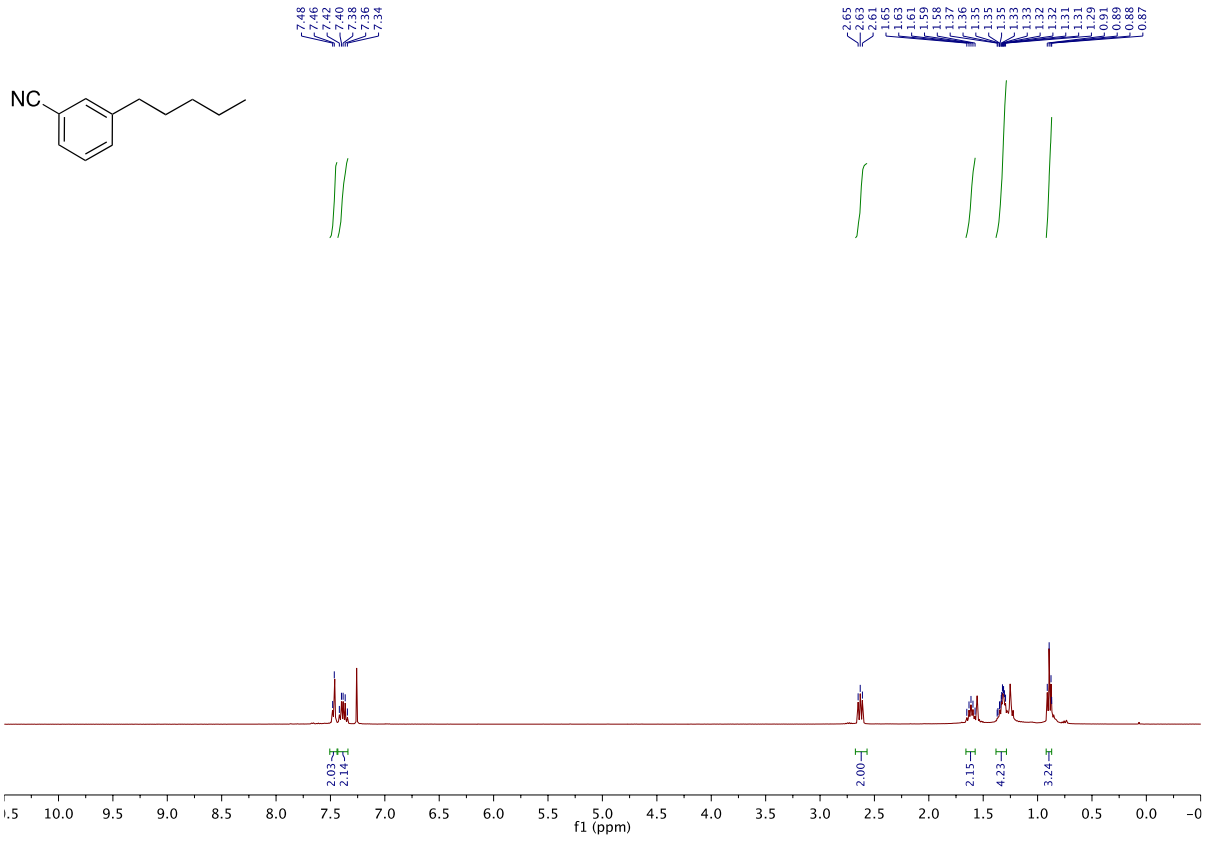


1-Pentyl-3-(trifluoromethyl)benzene

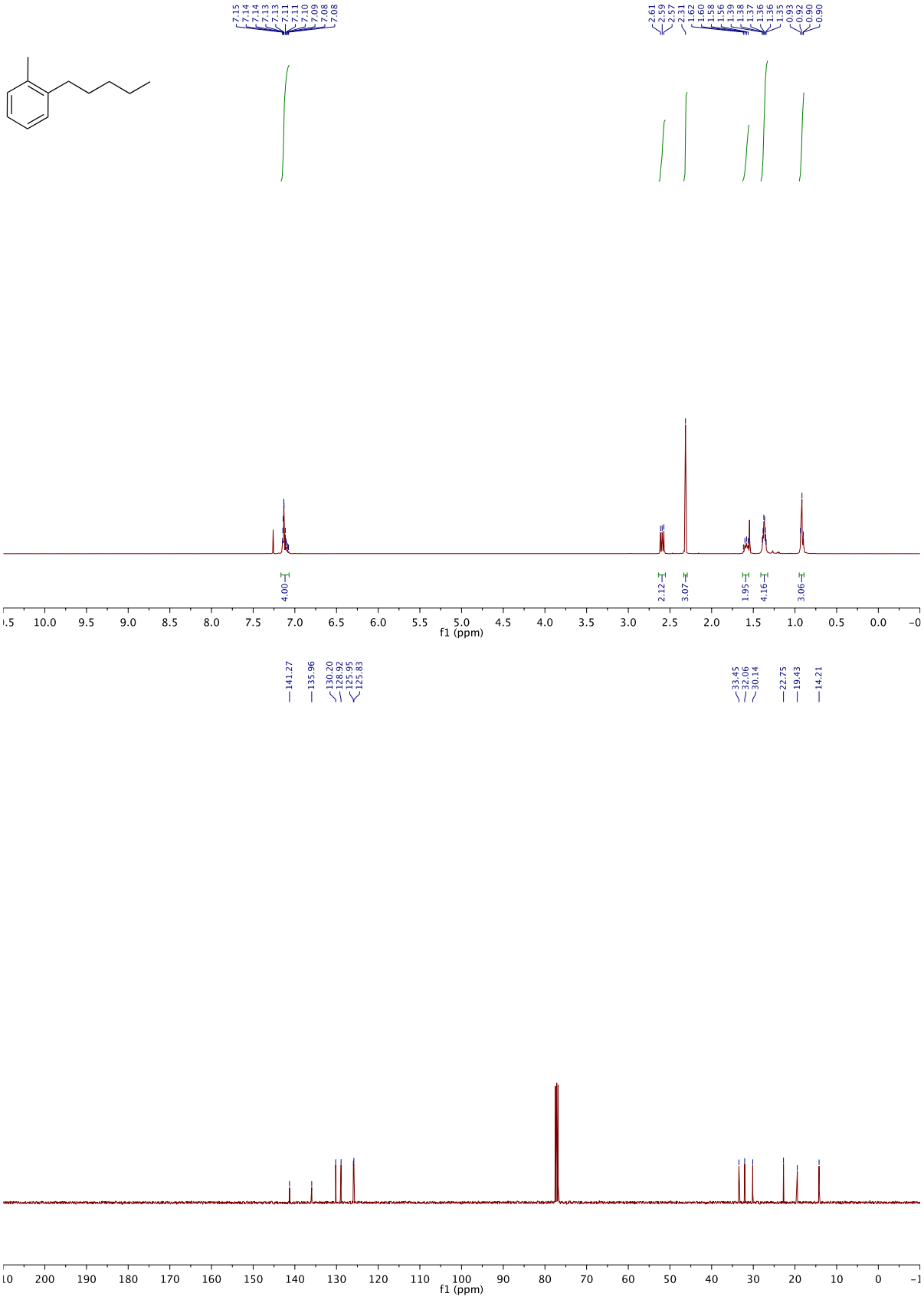




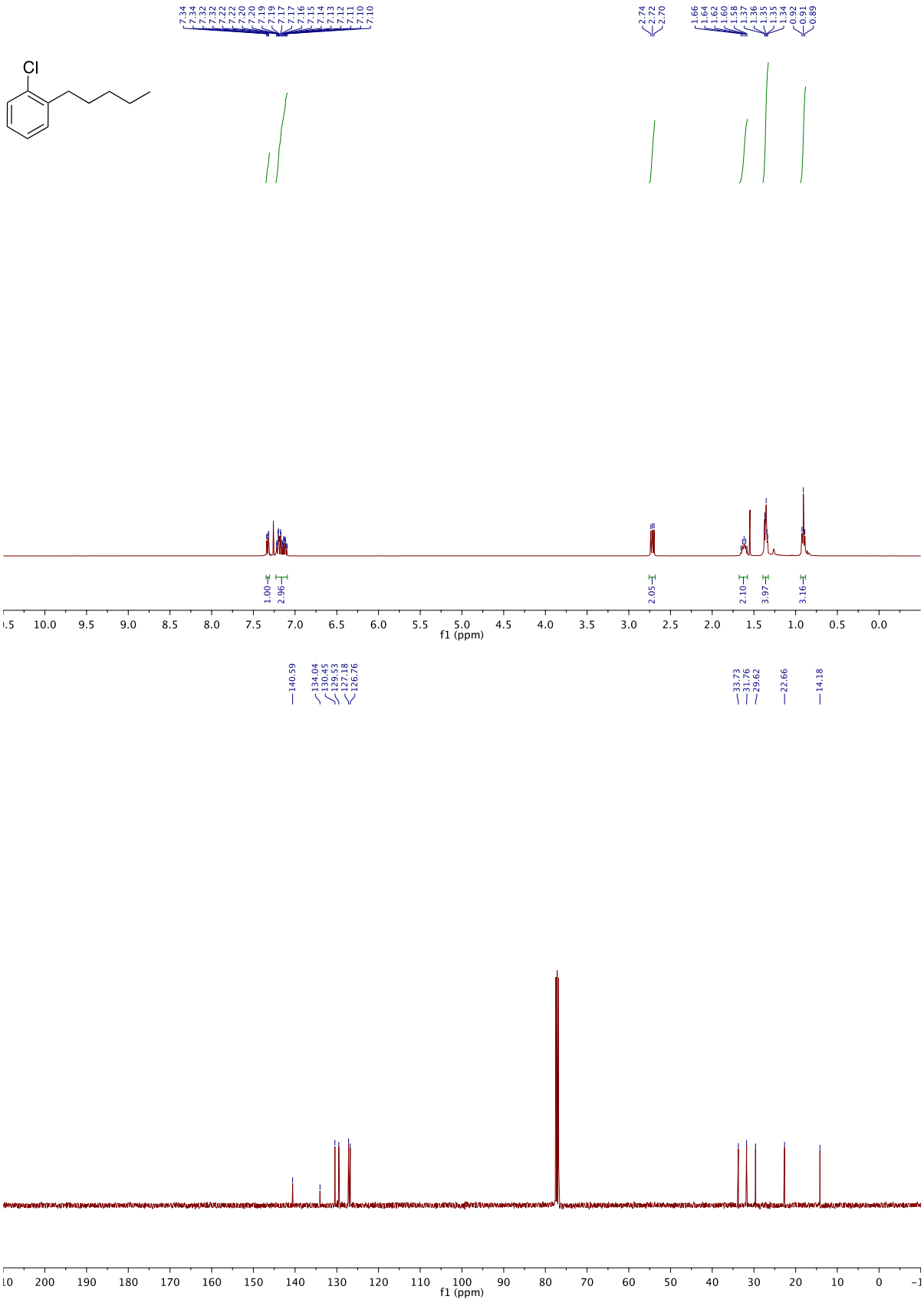
3-Pentylbenzonitrile



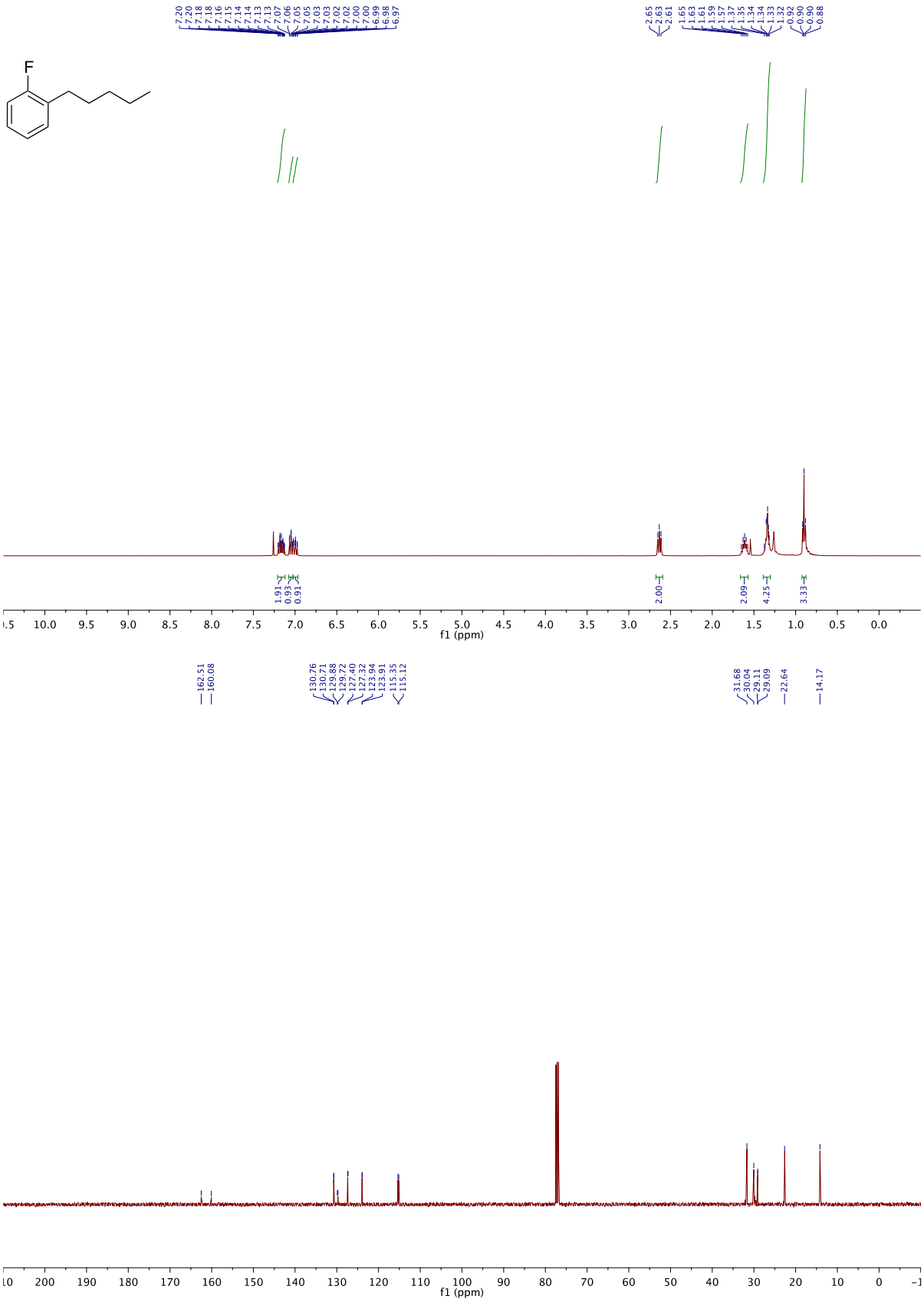
1-Methyl-2-pentylbenzene

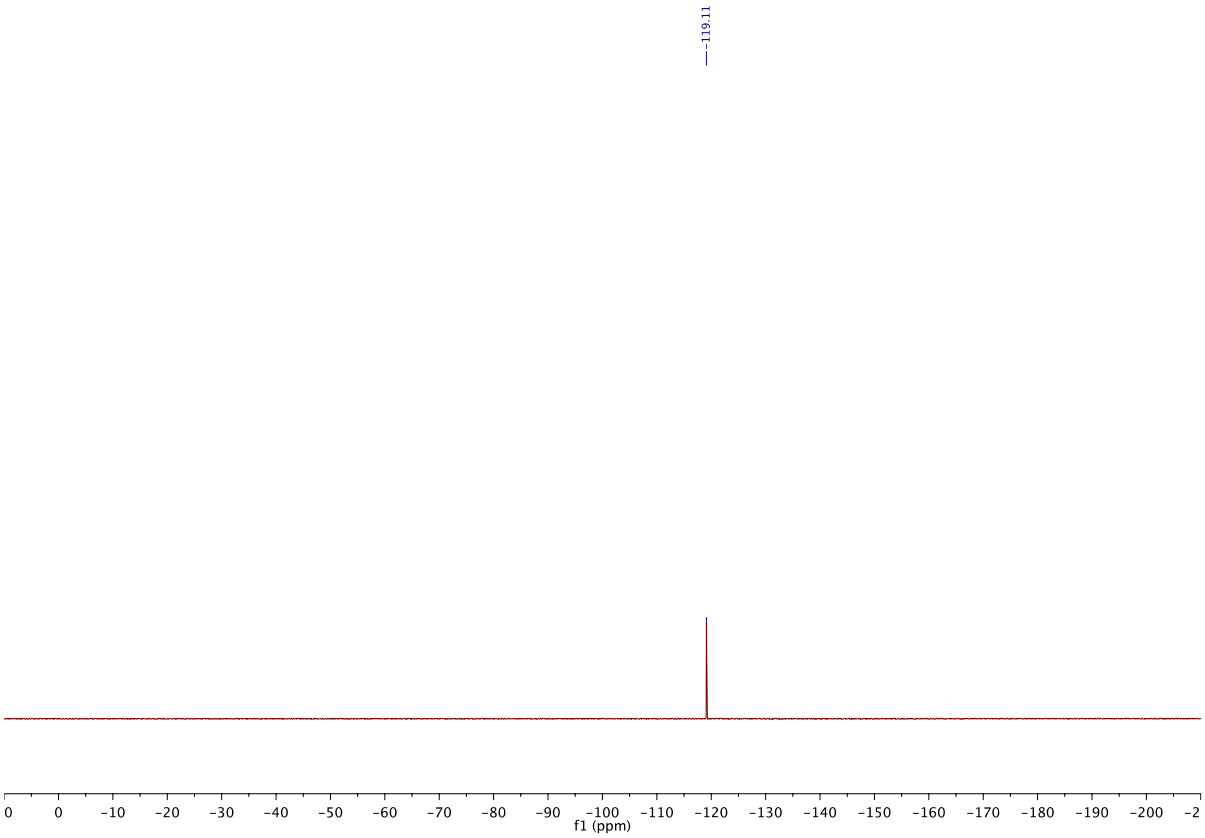


1-Chloro-2-pentylbenzene

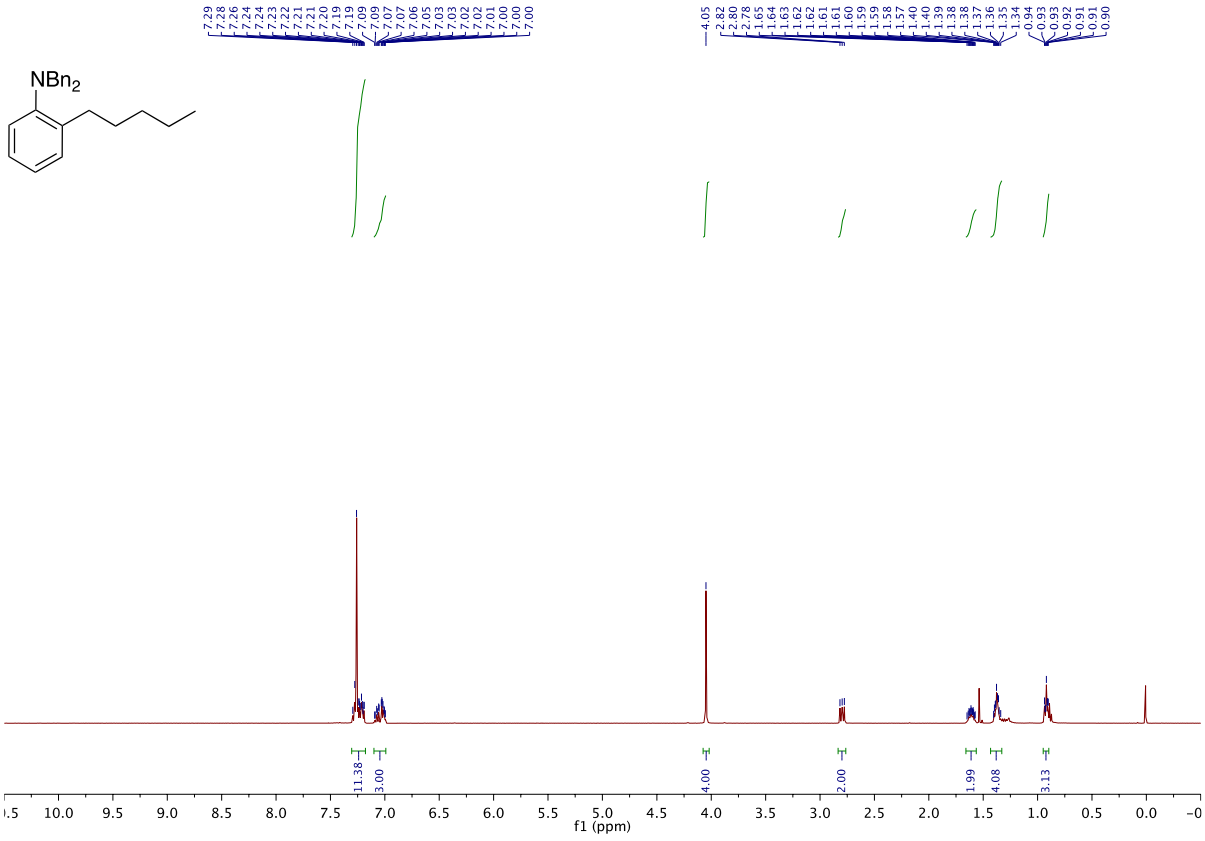


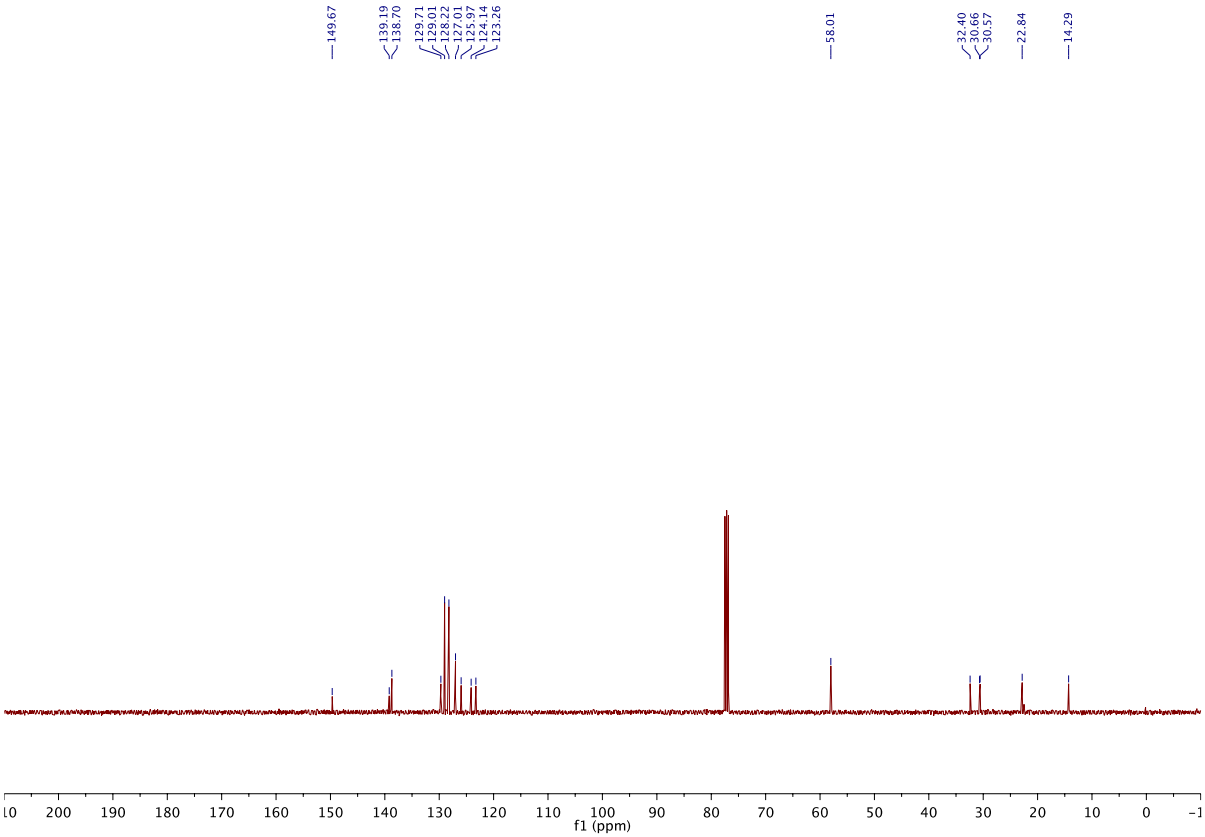
1-Fluoro-2-pentylbenzene



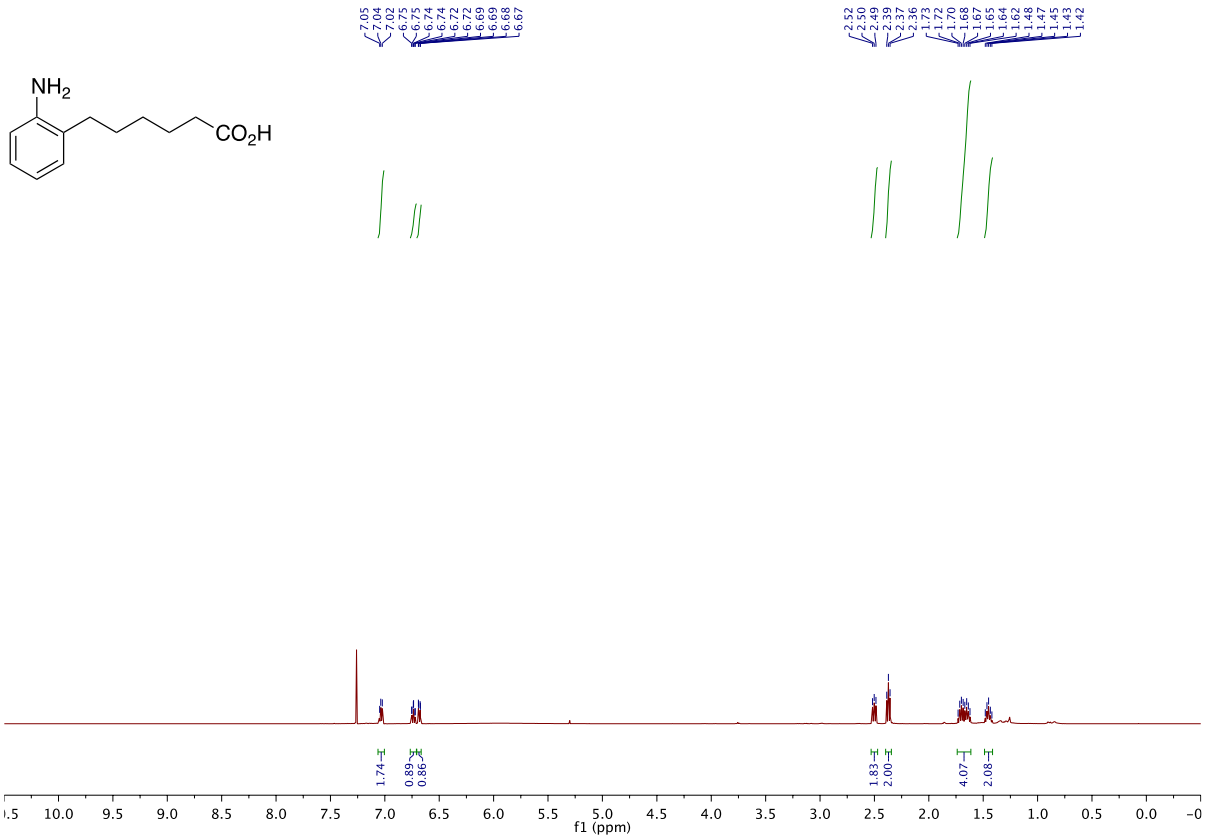


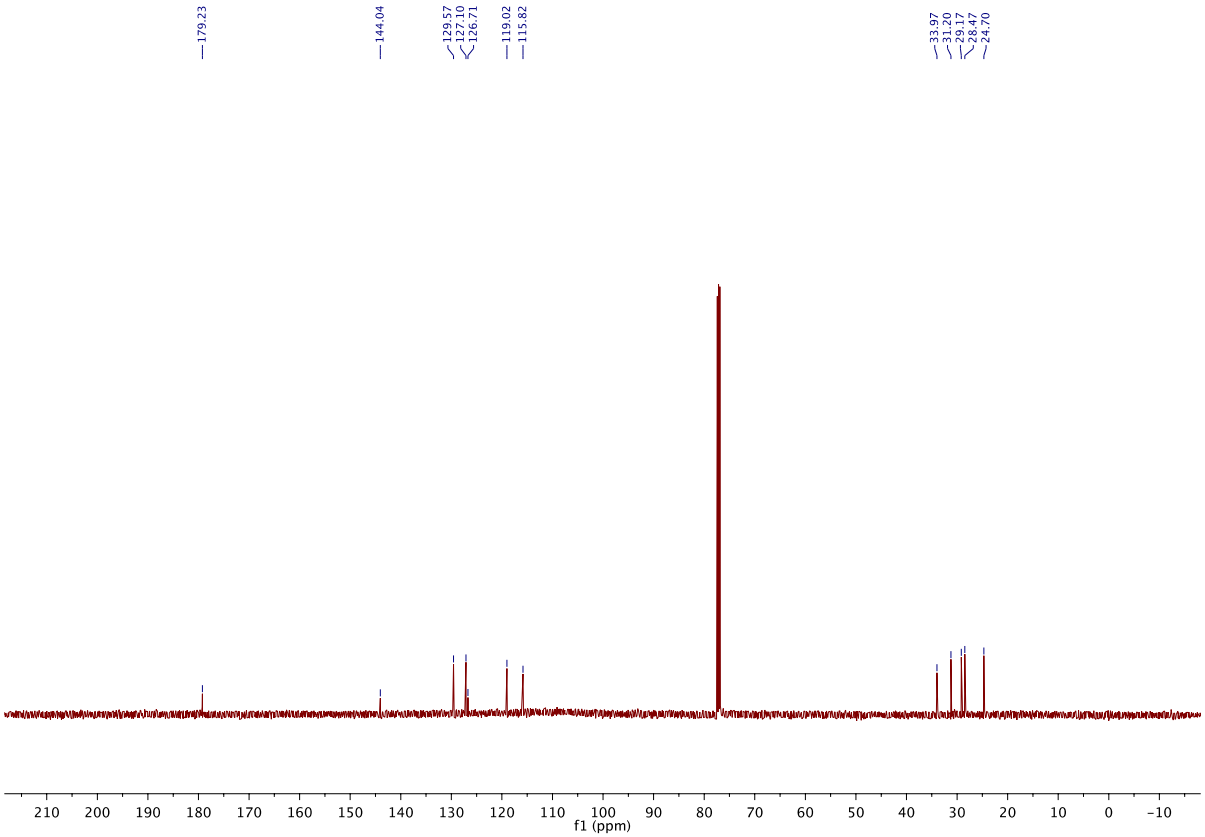
N,*N*-Dibenzyl-2-pentylaniline



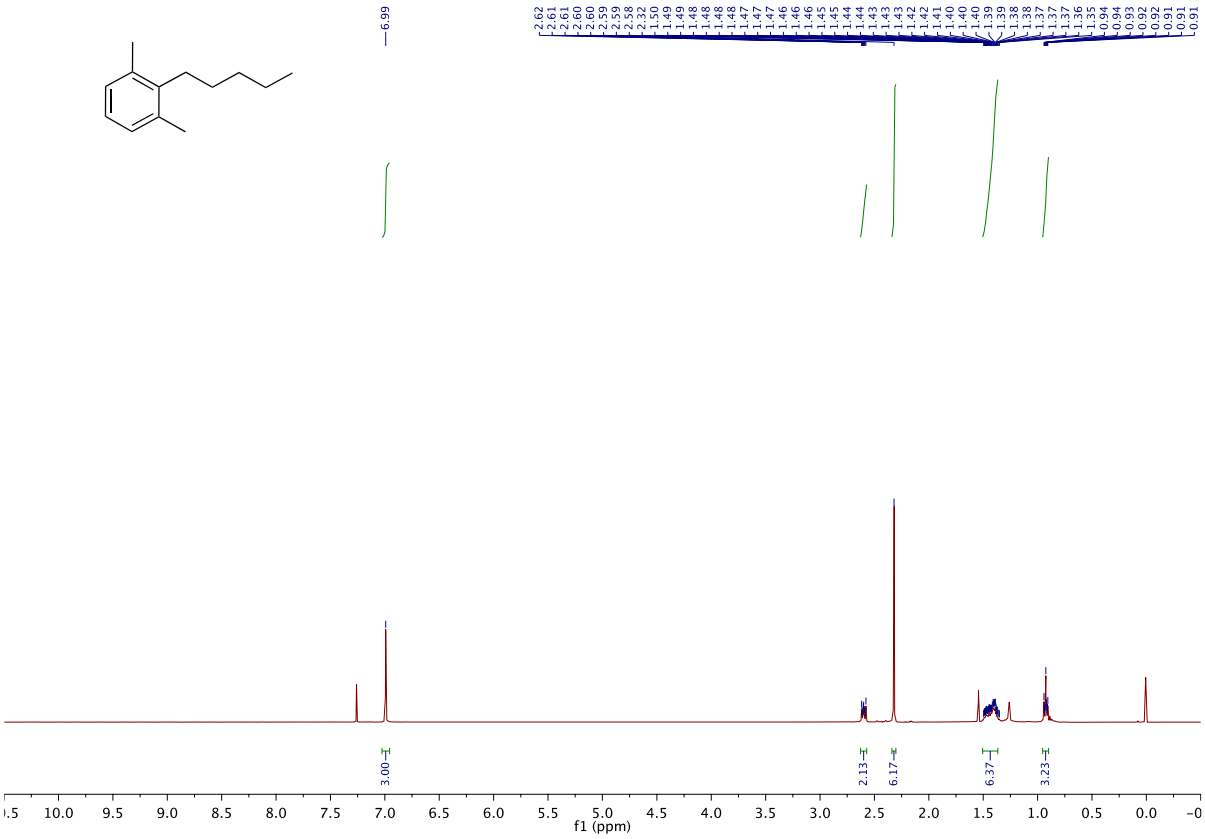


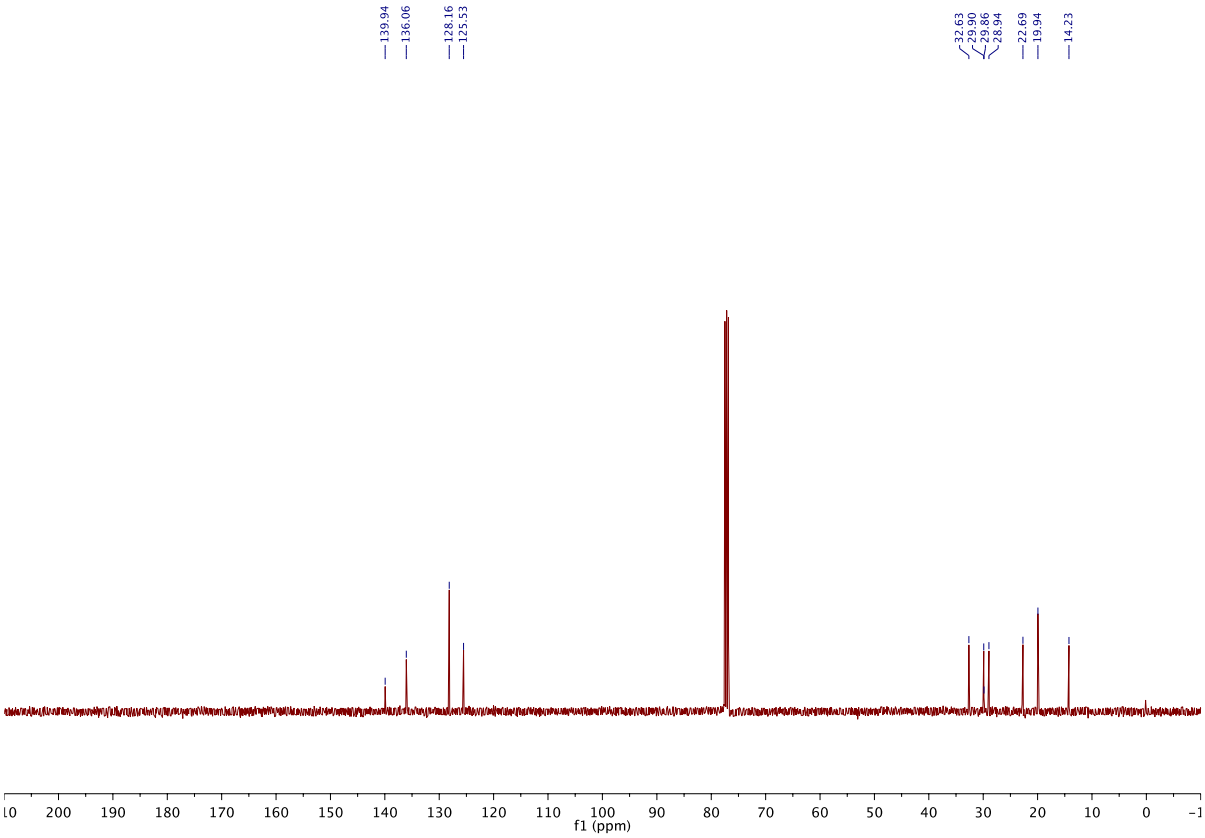
6-(2-Aminophenyl)hexanoic acid



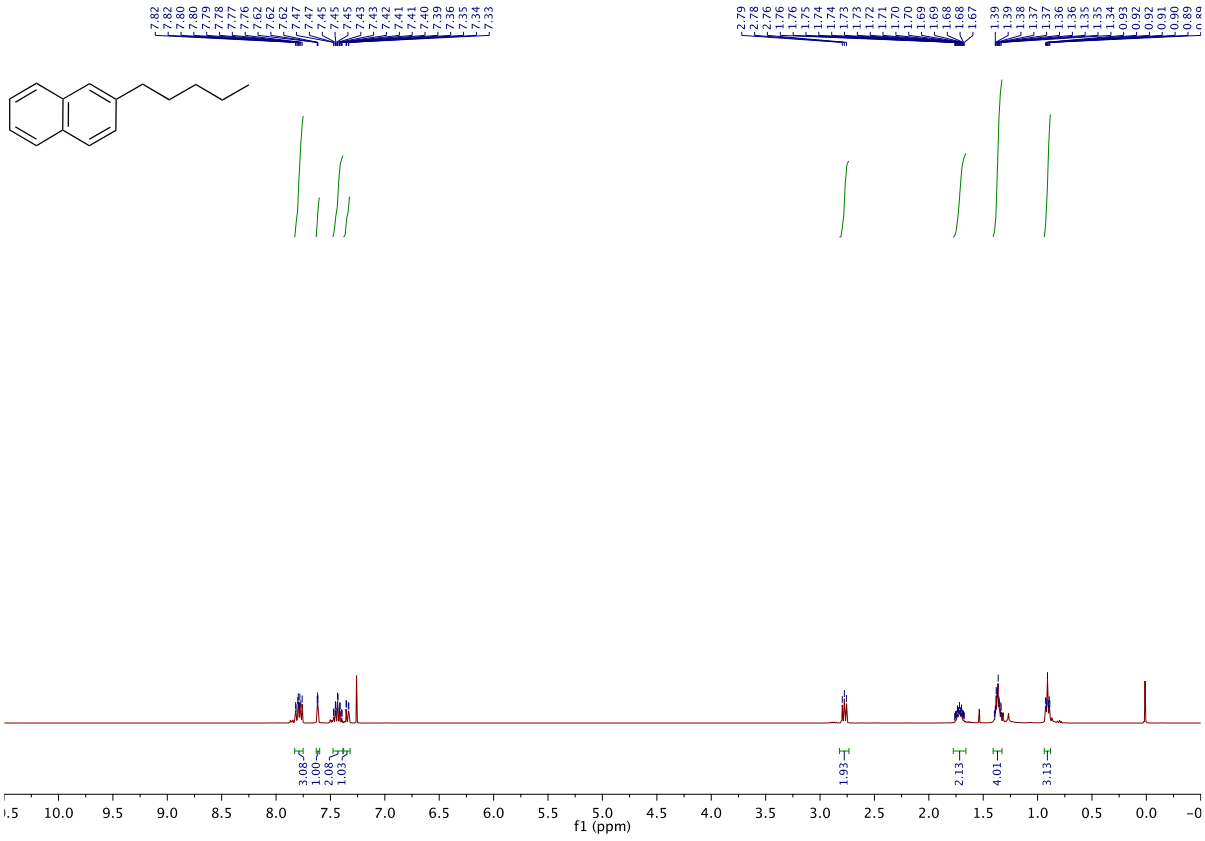


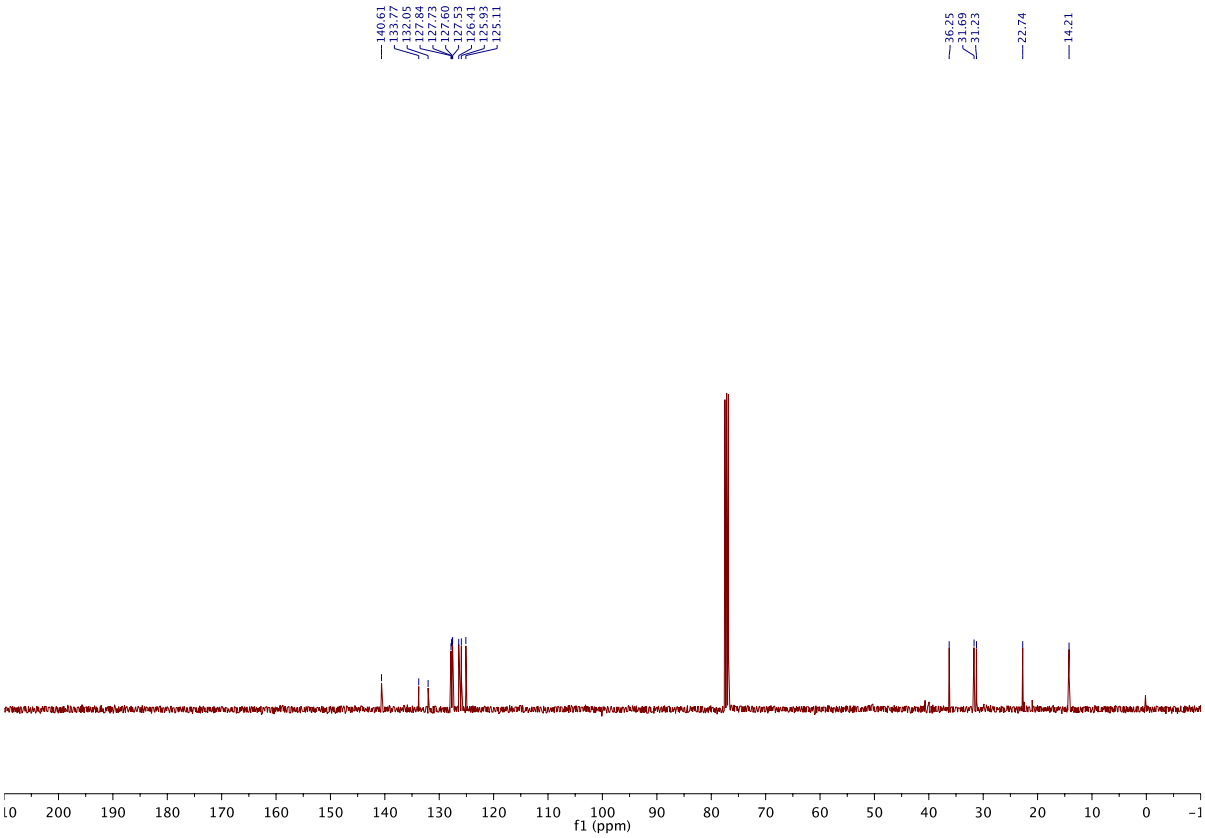
1,3-Dimethyl-2-pentylbenzene



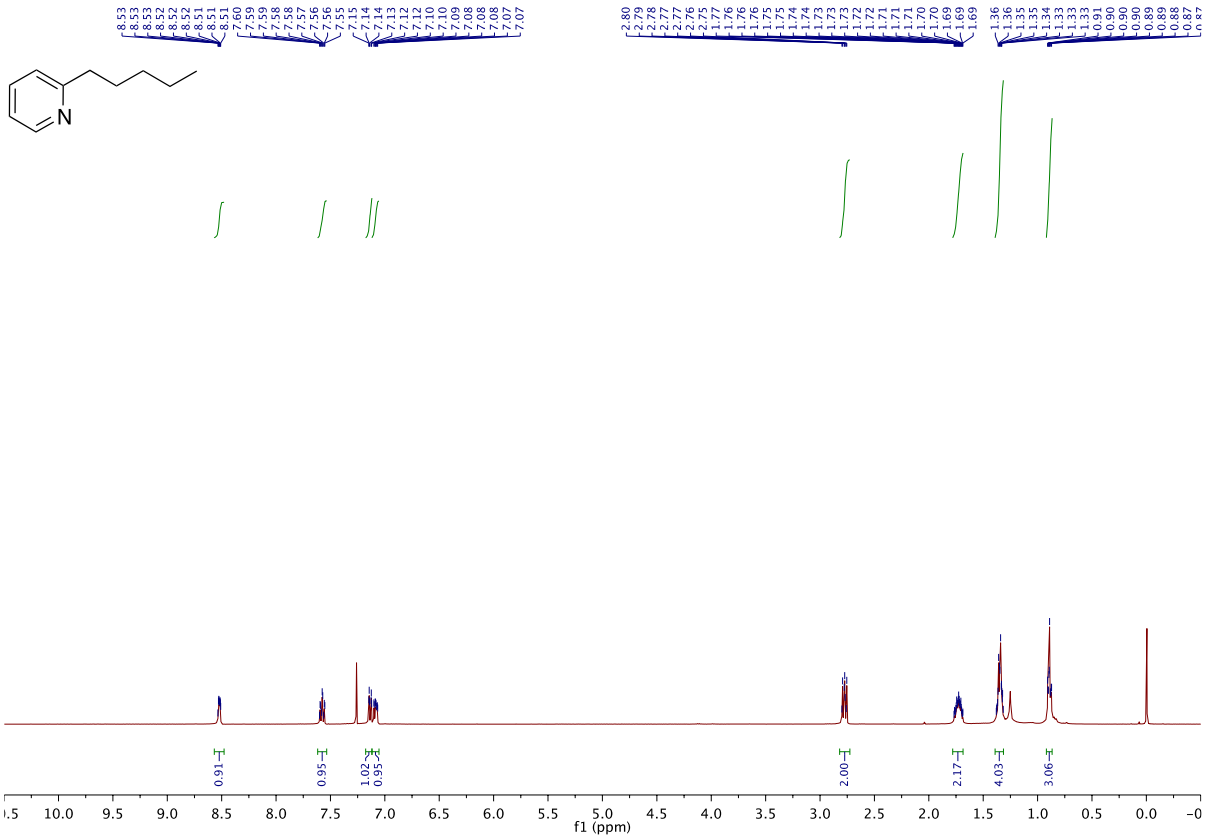


2-Pentylnaphthalene

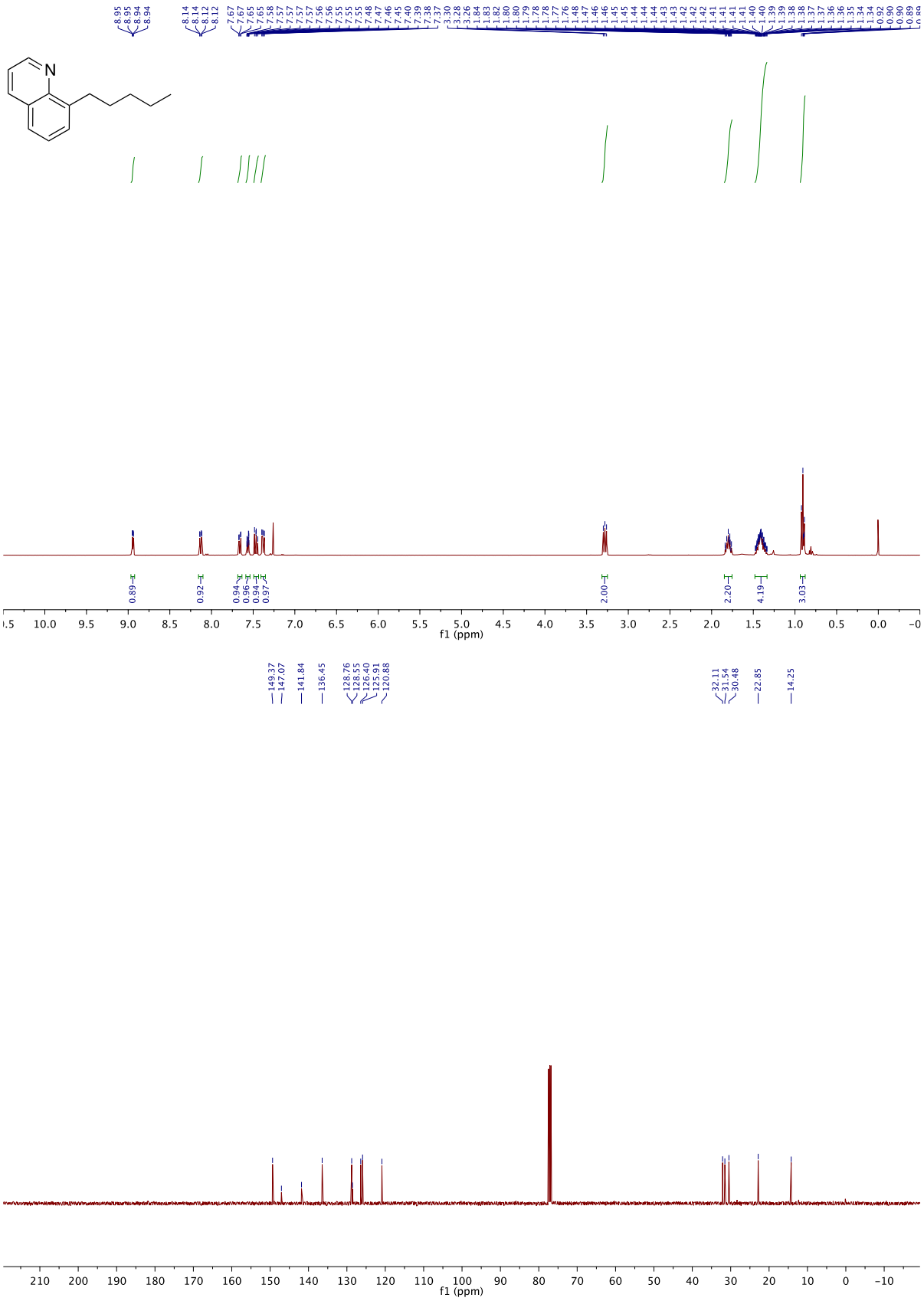




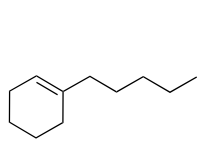
2-Pentylpyridine

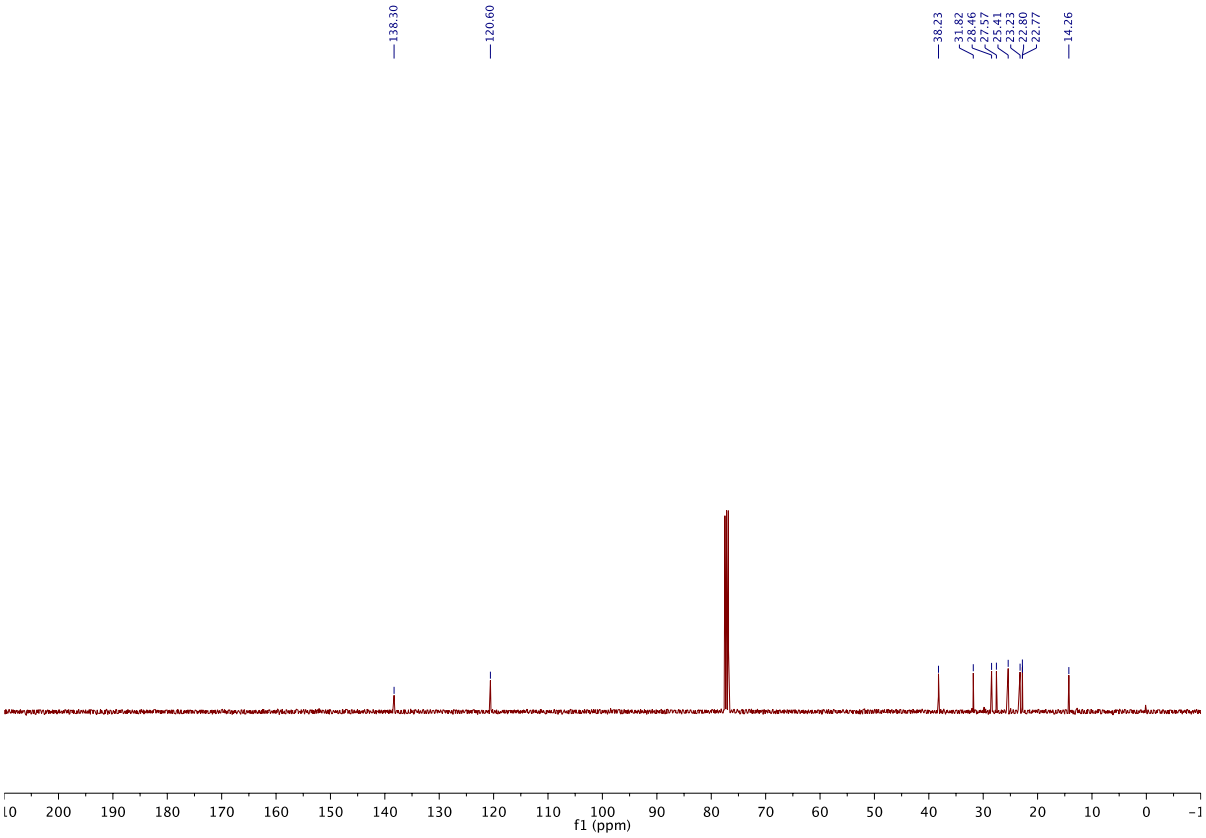


8-Pentylquinoline

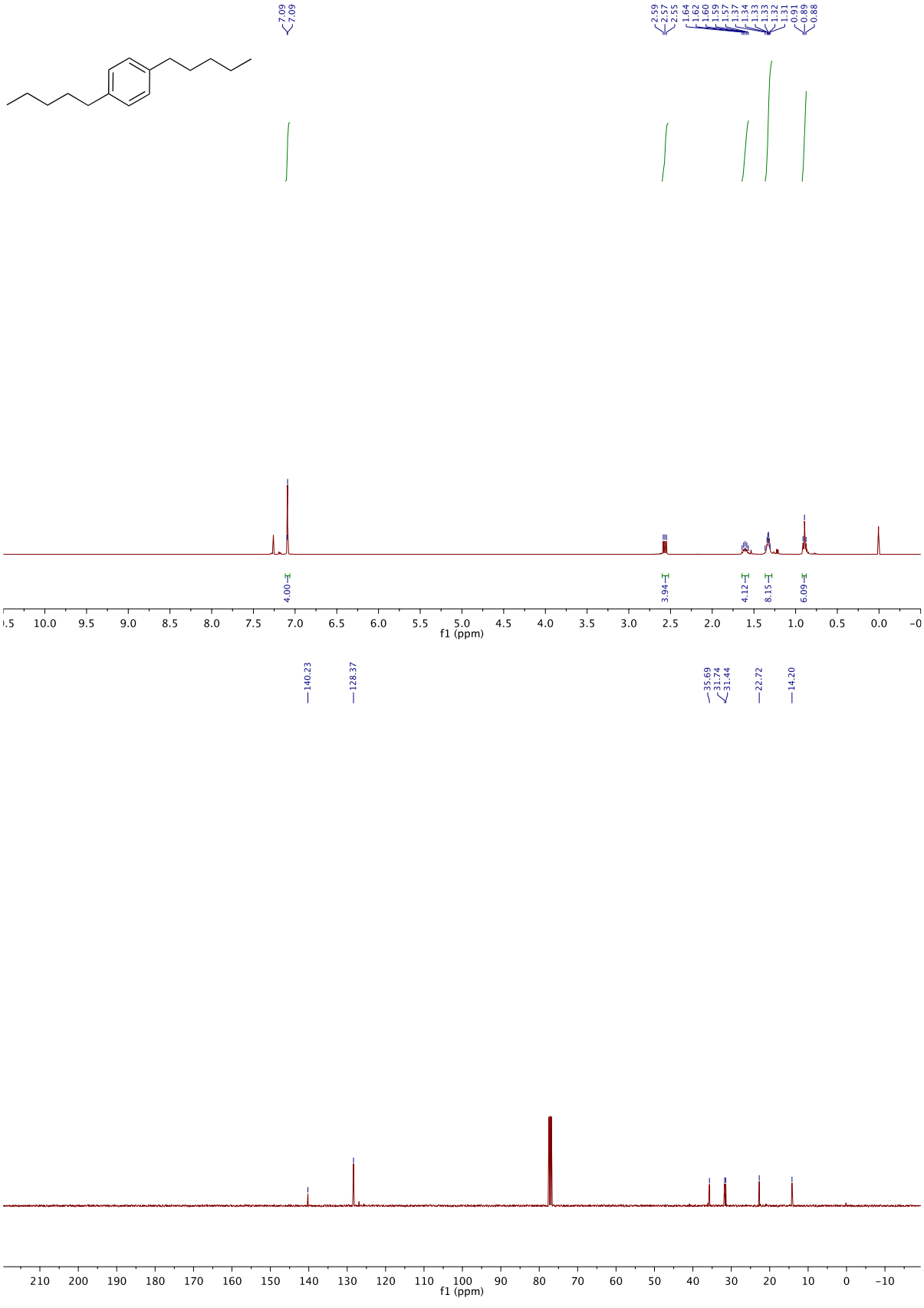


1-Pentylcyclohex-1-ene

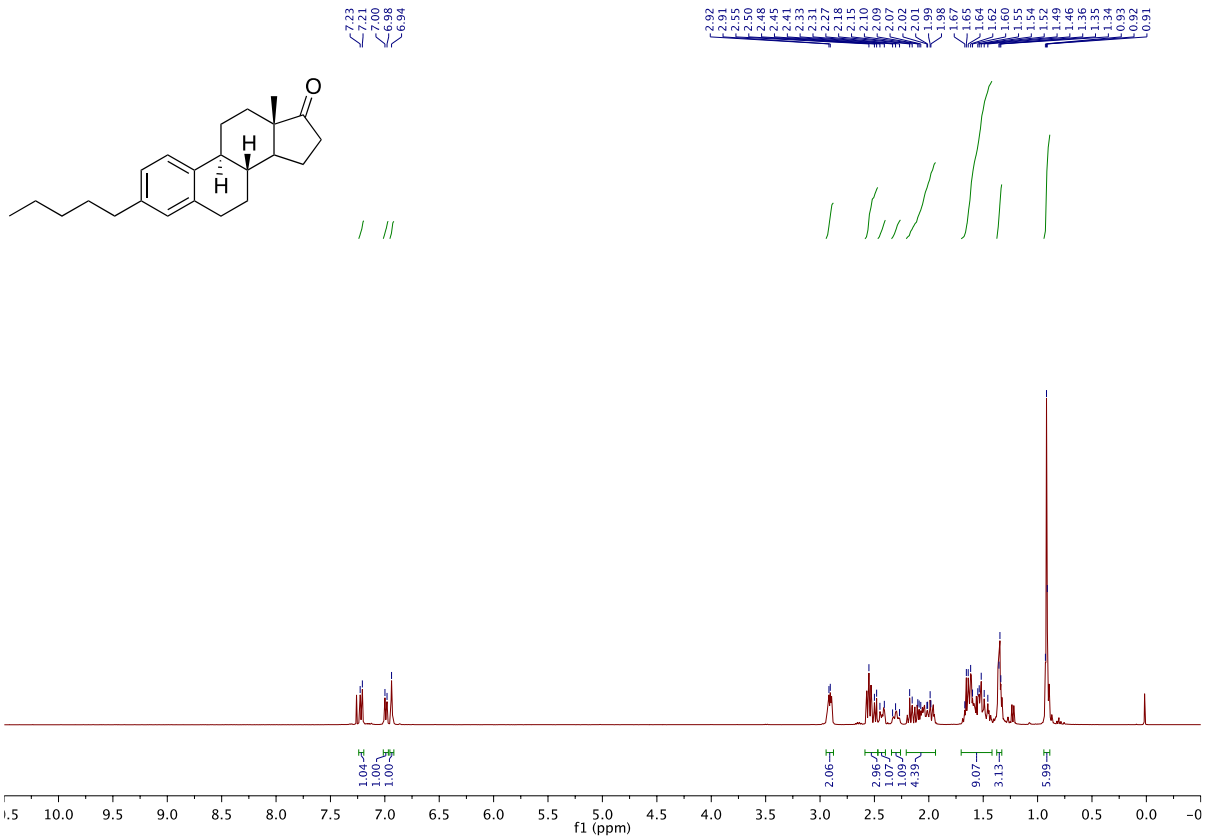


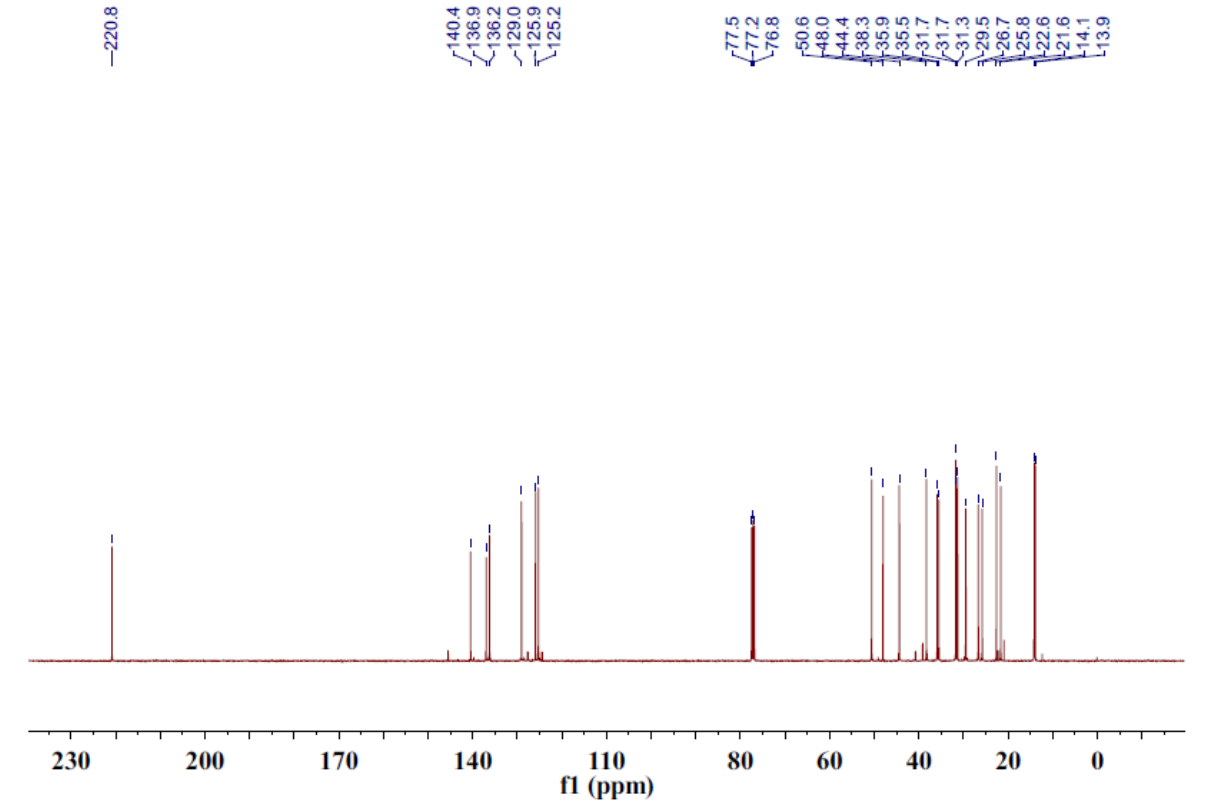


1,4-Dipentylbenzene

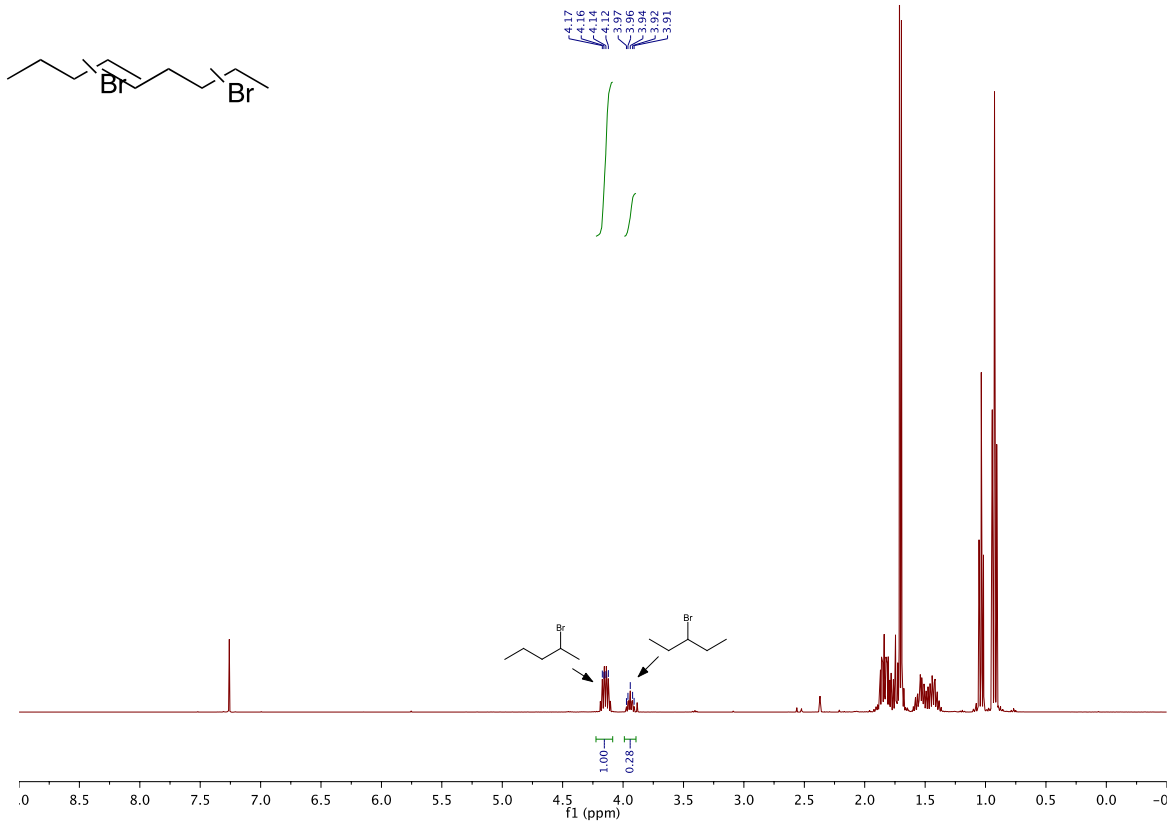


1-Pentyl estra-1,3,5(10)-trien-17-one

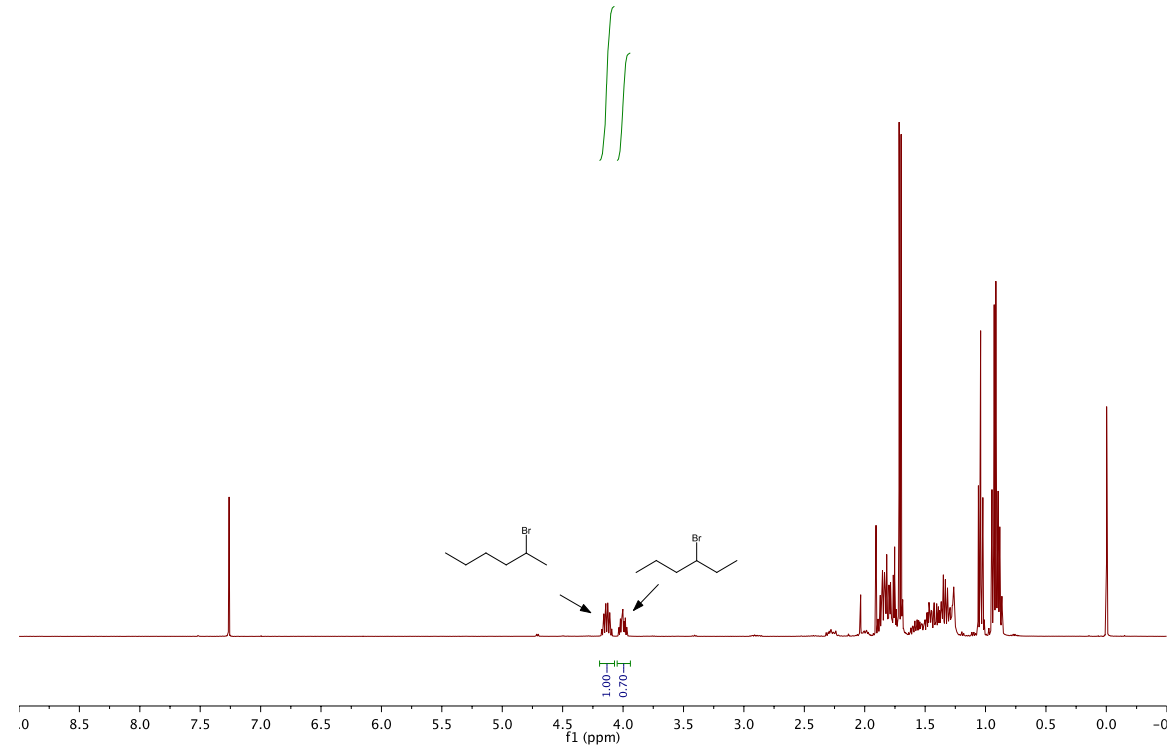




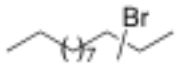
Mixture of bromopentanes

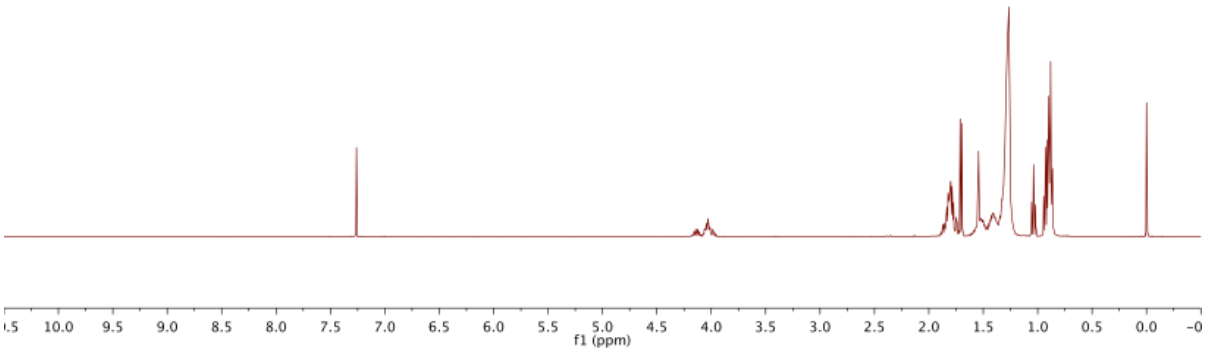


Mixture of bromohexanes

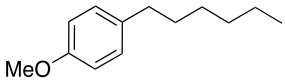


Mixture of bromododecanes

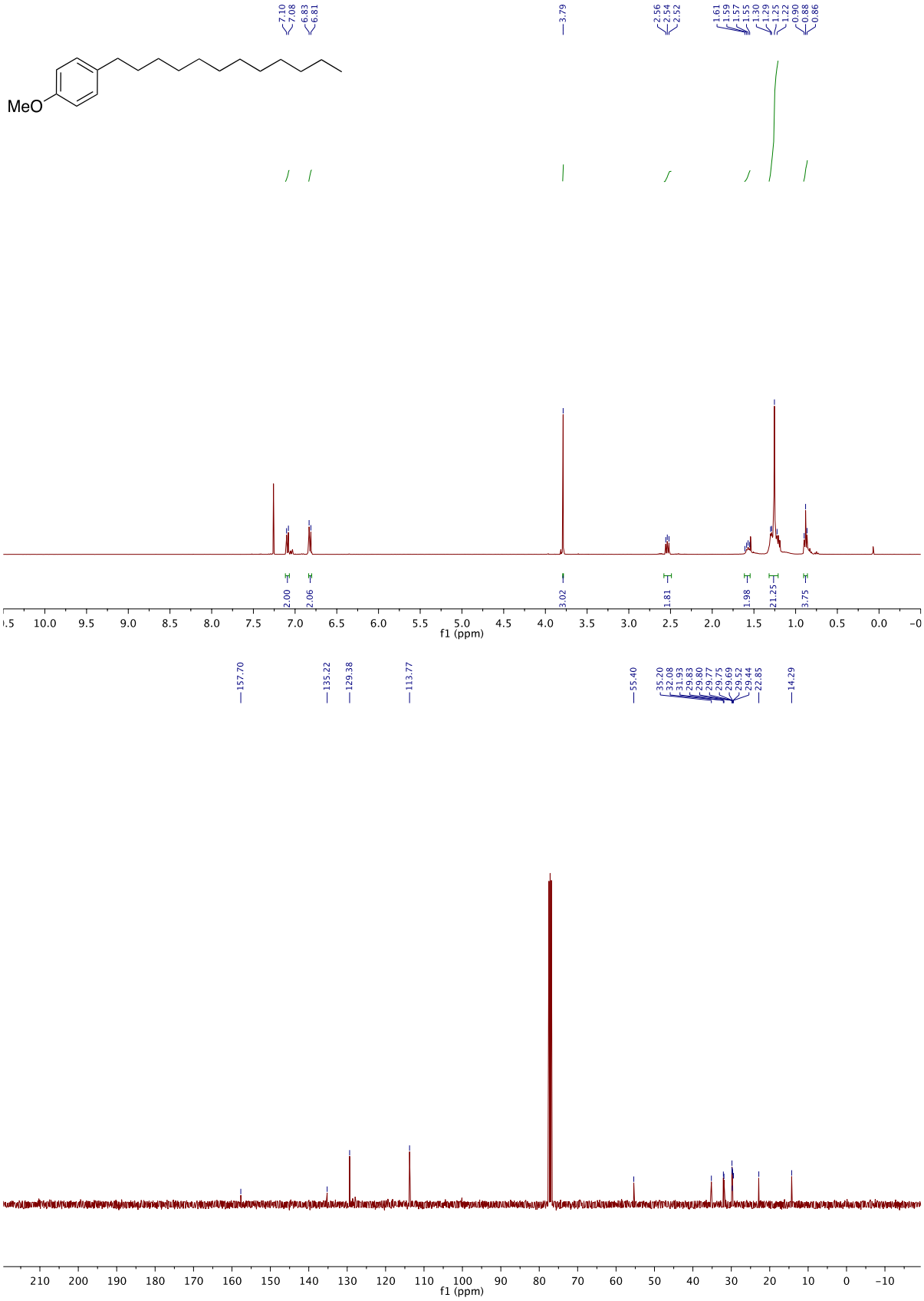




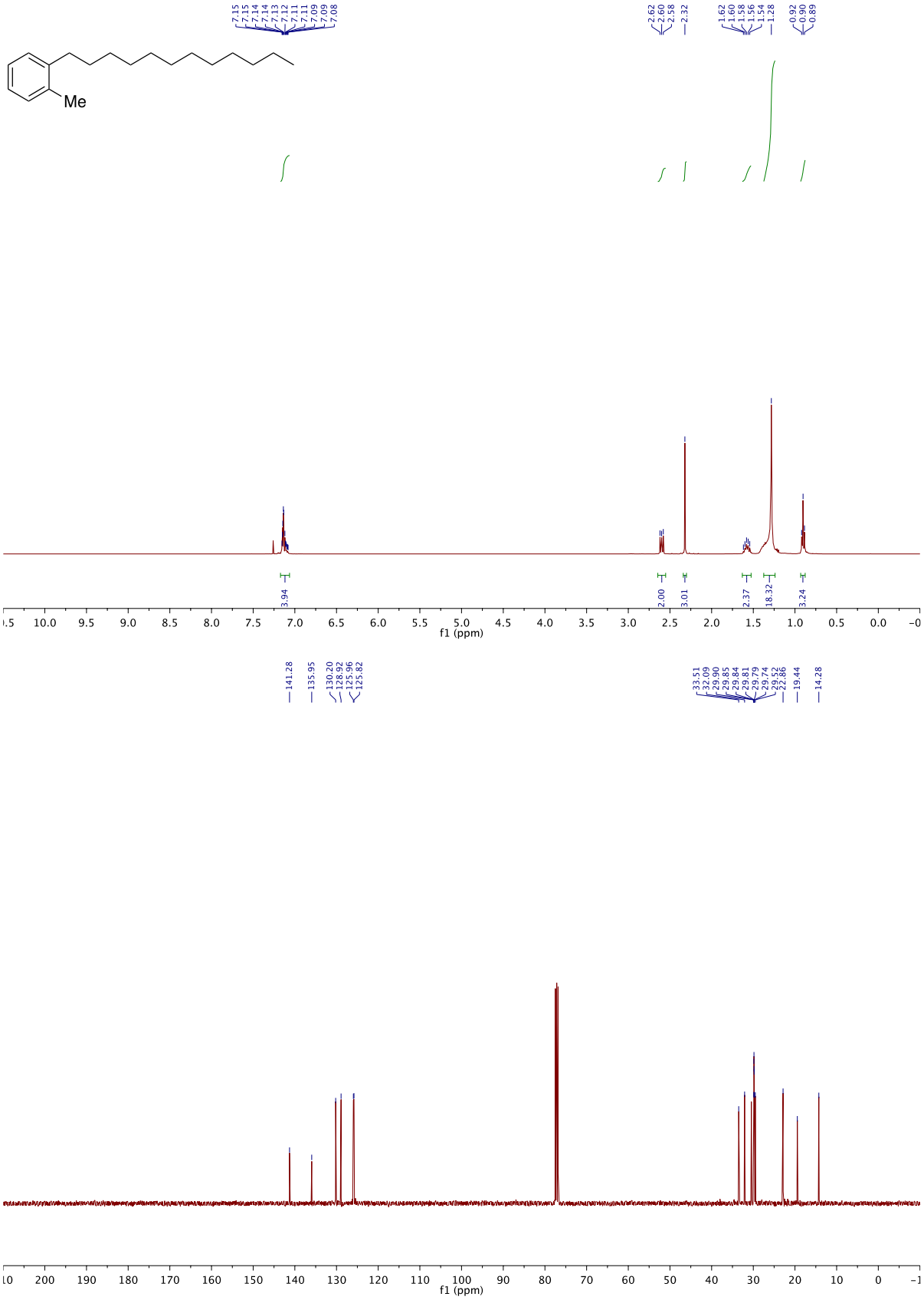
1-Hexyl-4-methoxybenzene



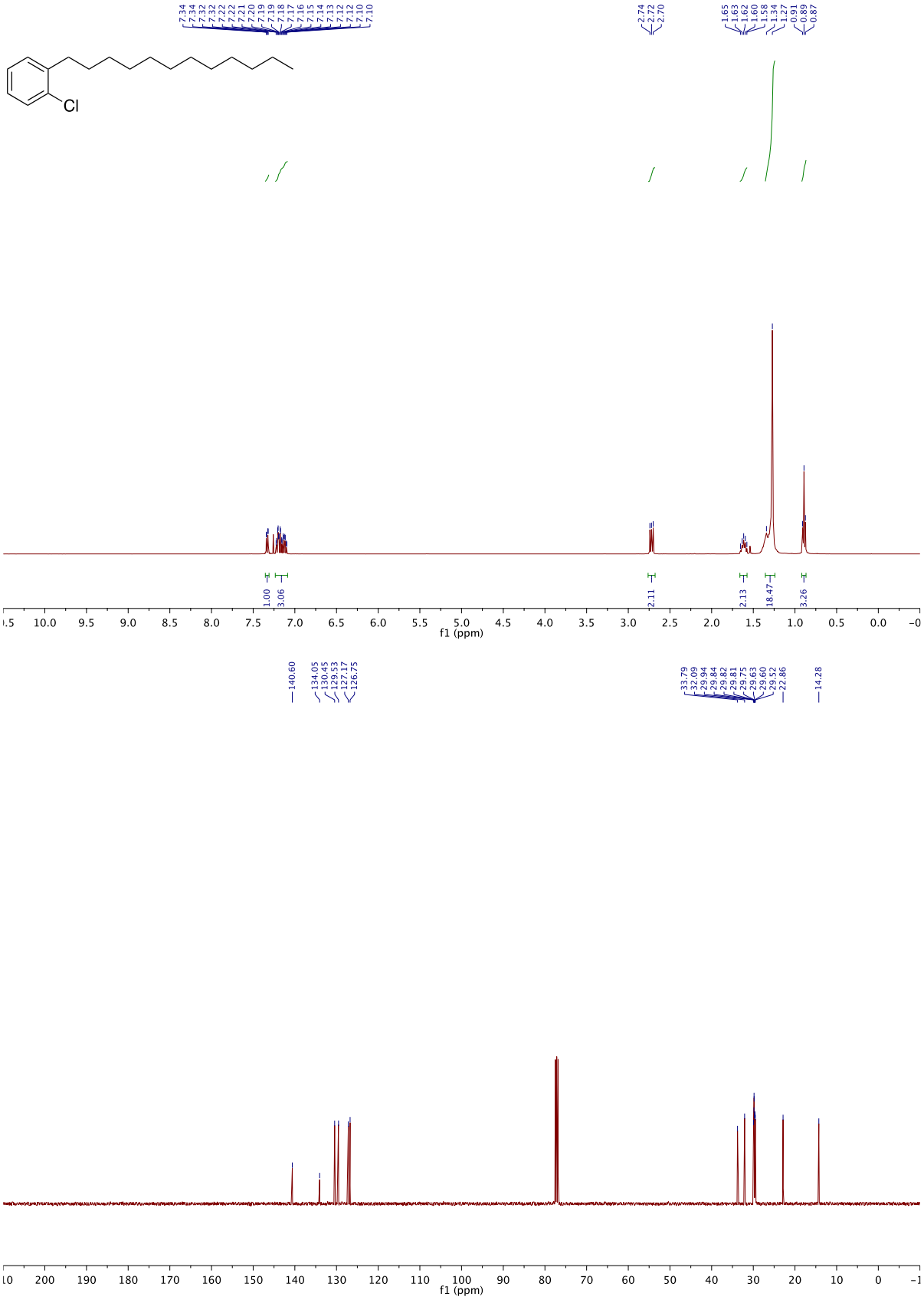
1-Dodecyl-4-methoxybenzene



1-Dodecyl-2-methylbenzene

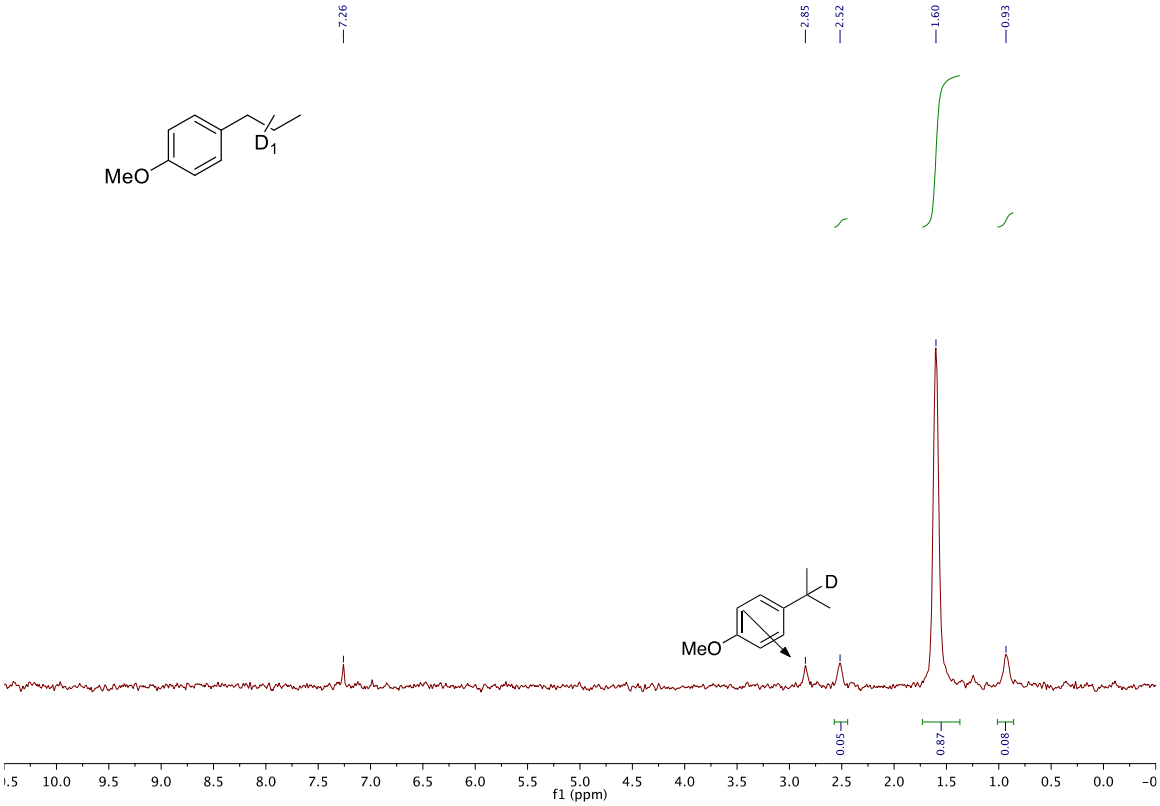


1-Chloro-2-dodecylbenzene

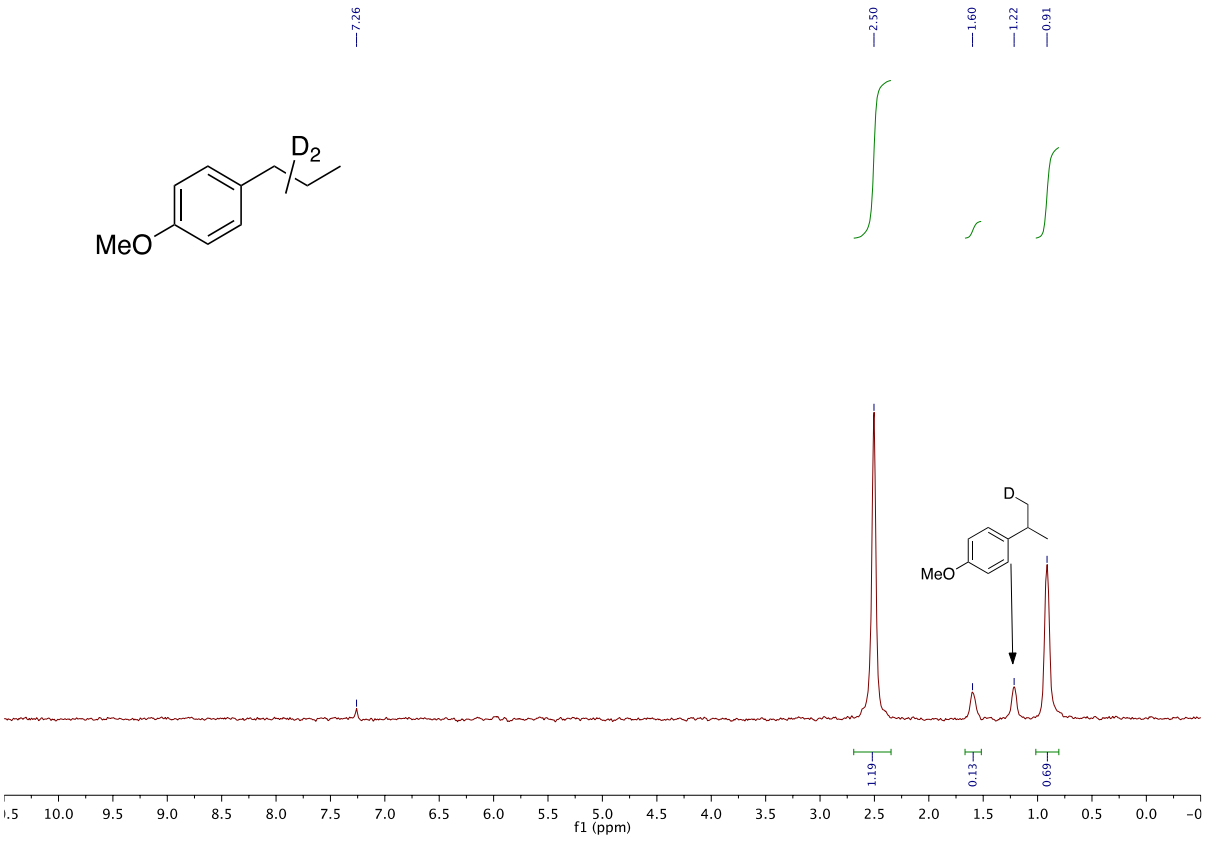


^{2}H NMR spectra

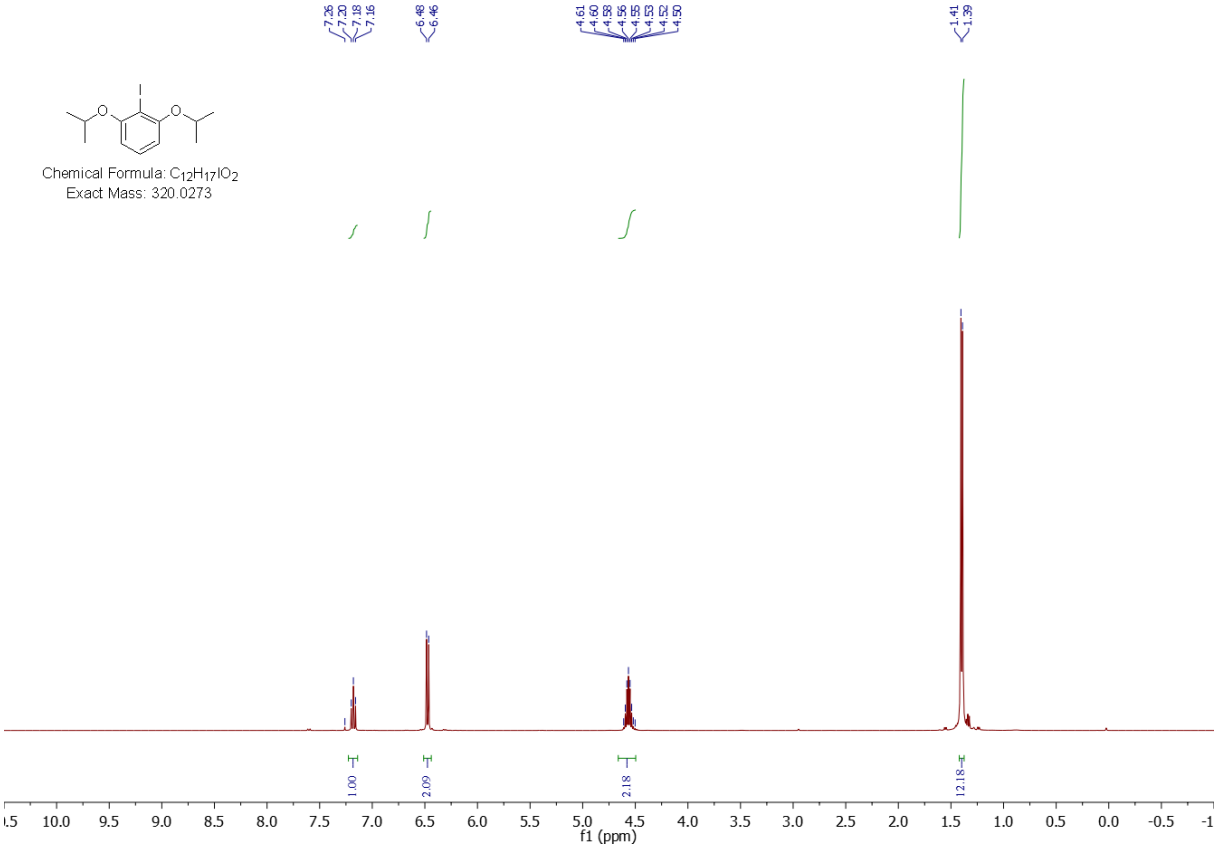
From 2-bromopropane-2-d_1



From 1-bromopropane-1,1-d_2



Chapter 3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7.20
7.18
7.16
6.48
6.46
4.61
4.60
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4.56
4.55
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4.52
4.50
1.41
1.39
I
O
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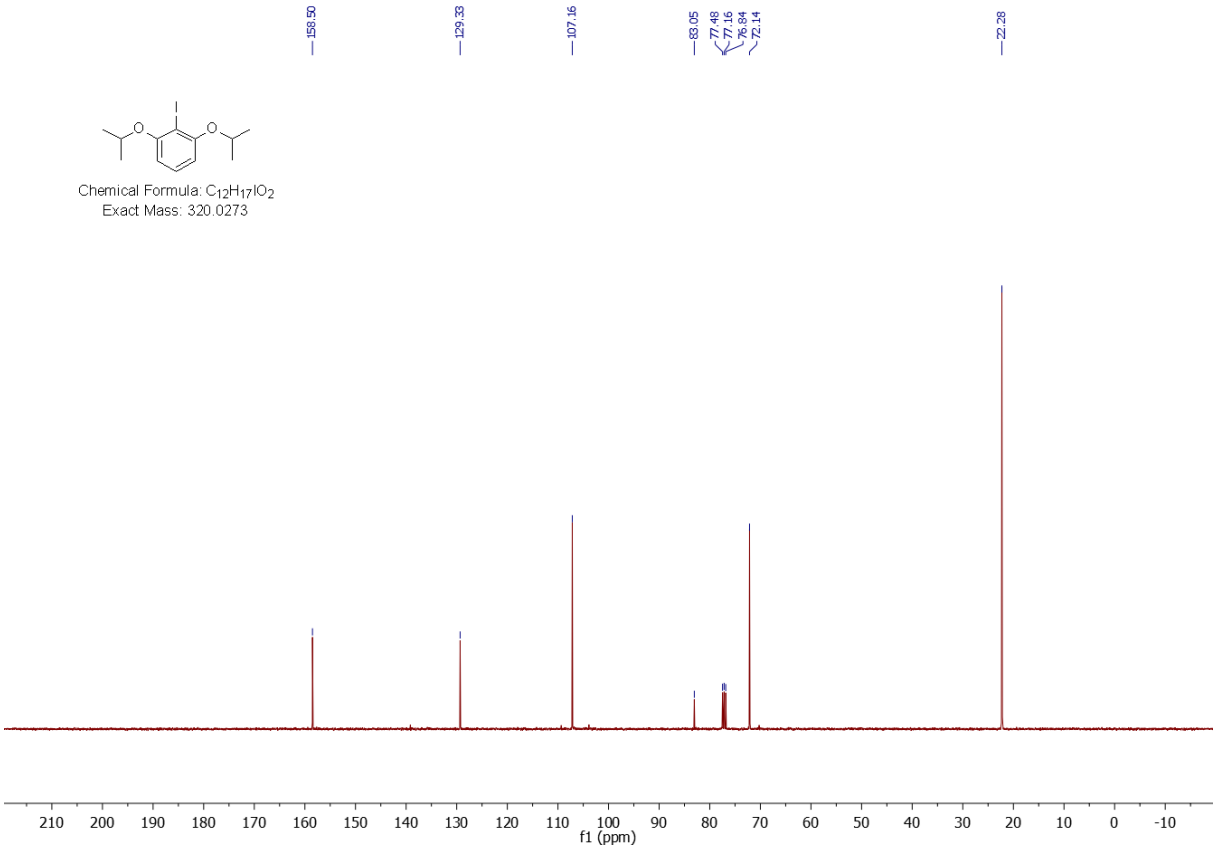
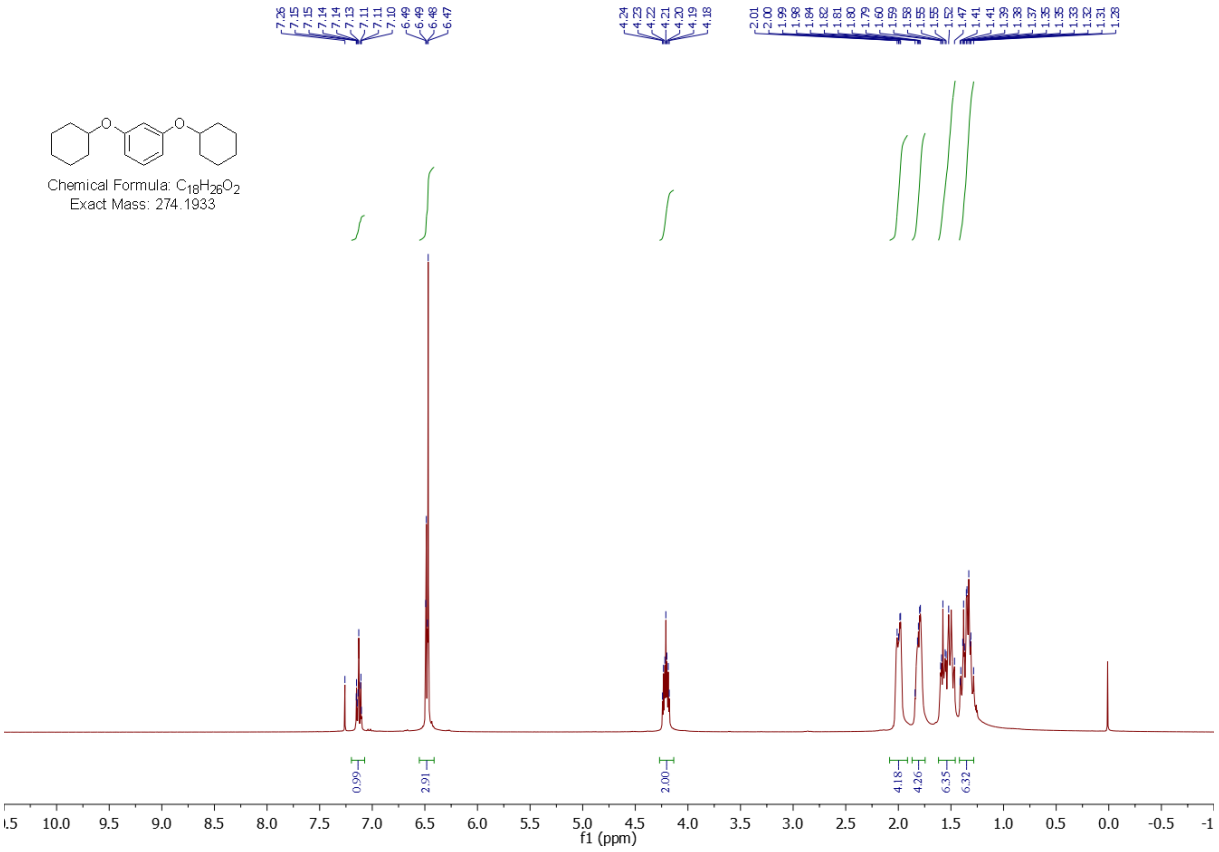
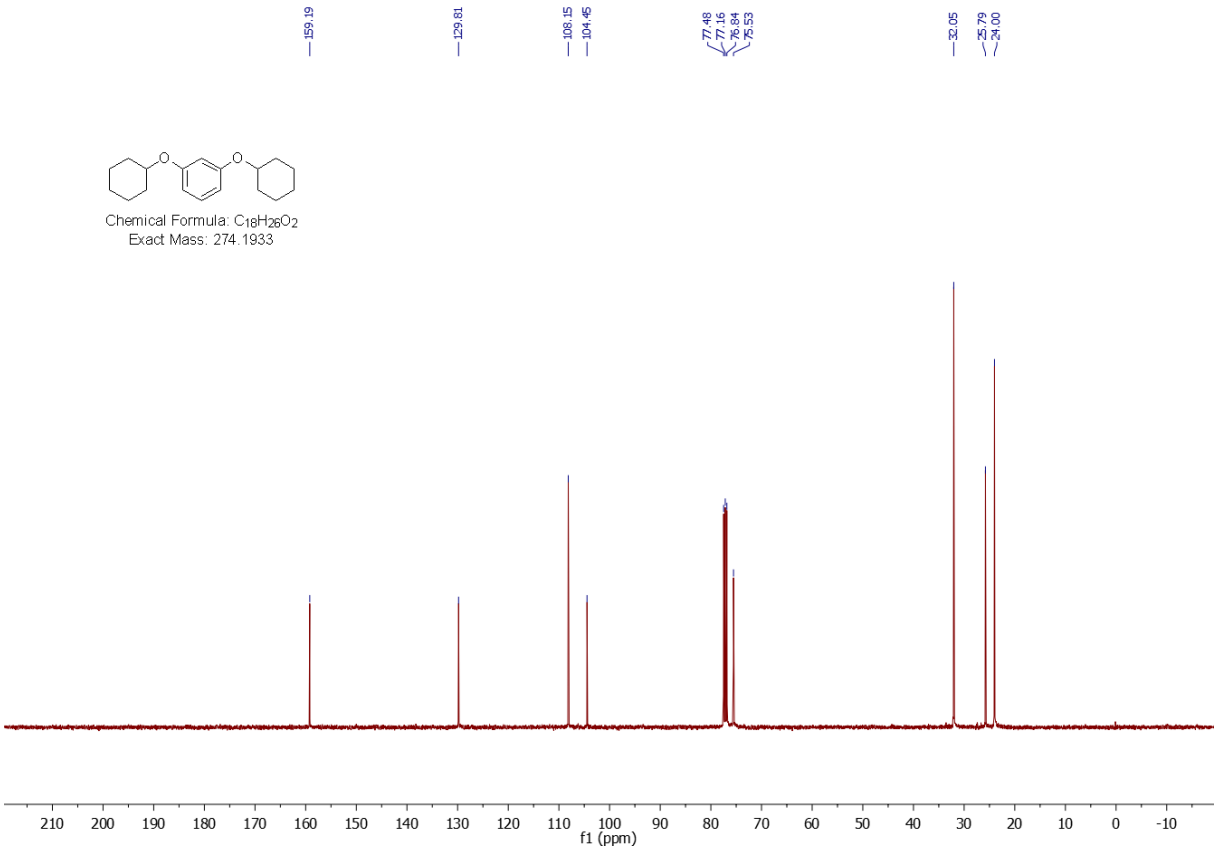
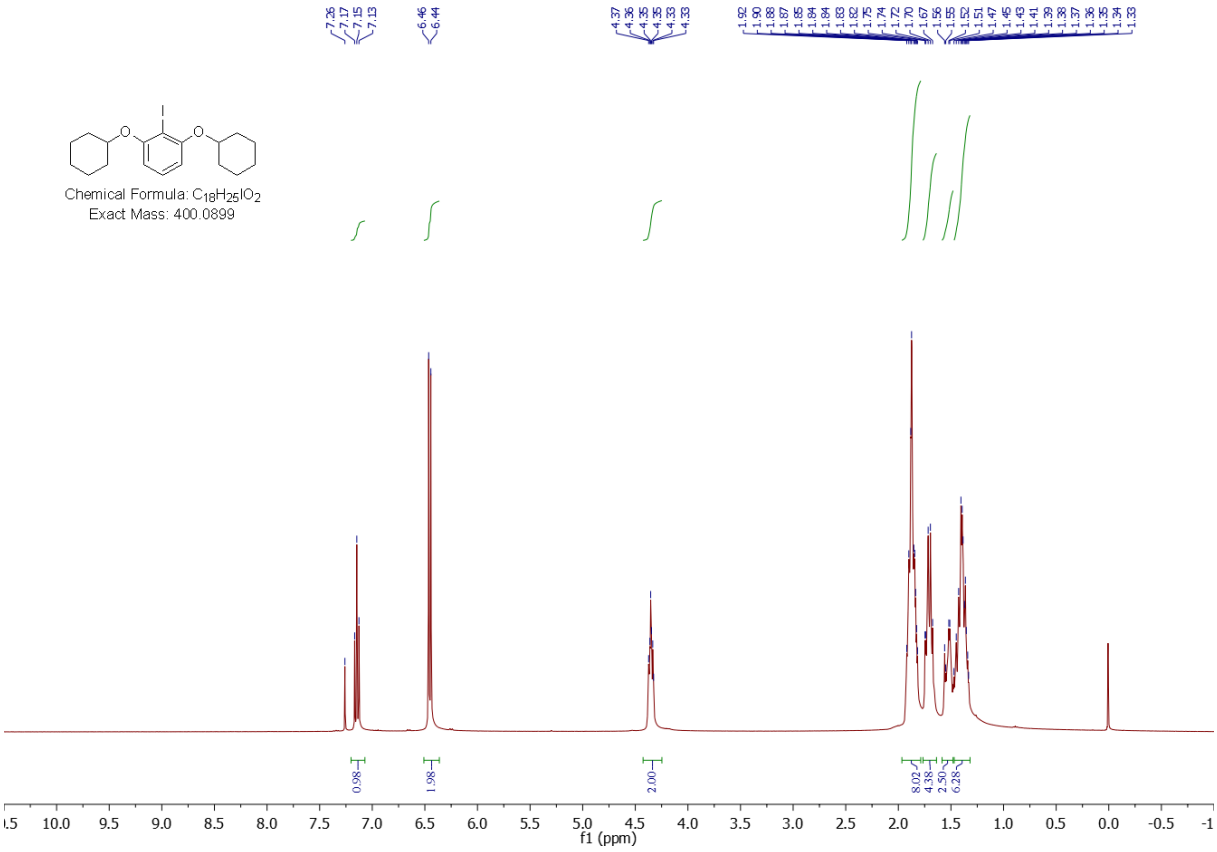
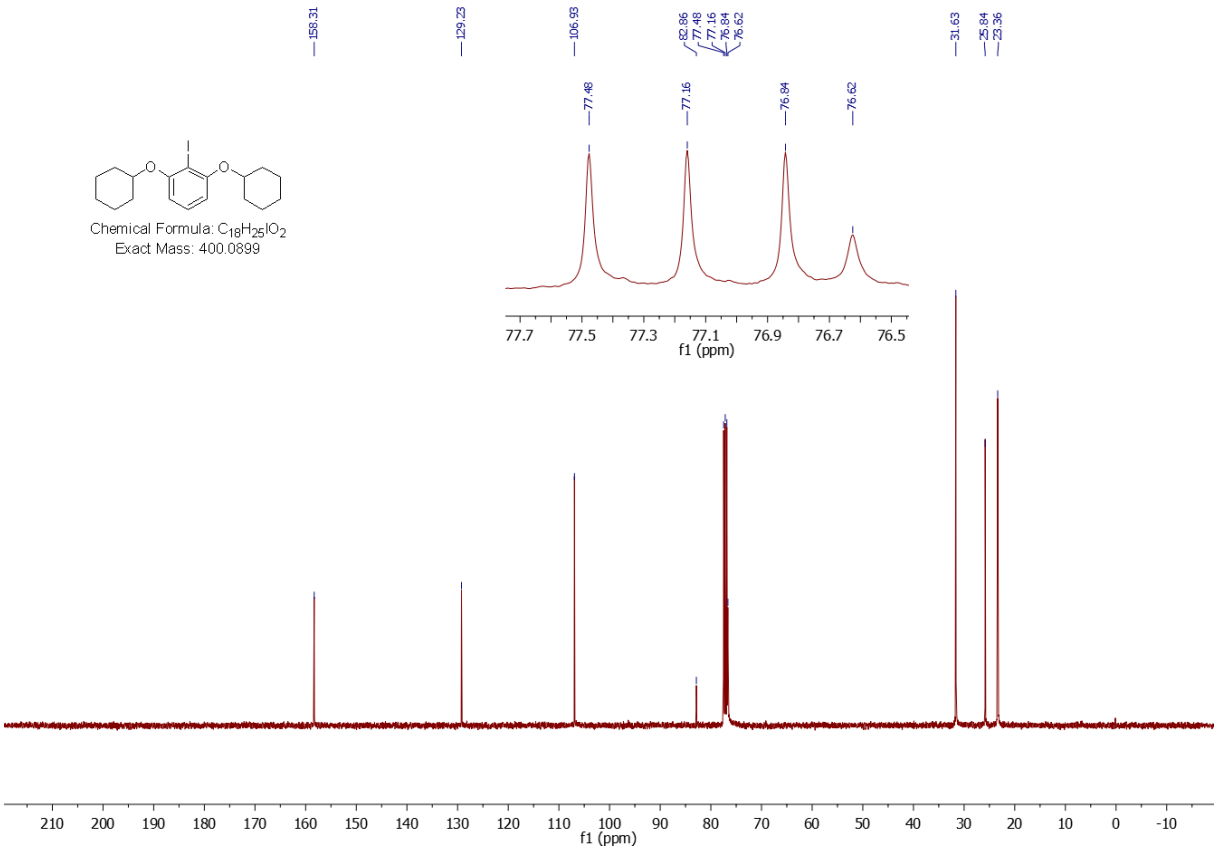
Exact Mass: 320.0273
1.00
2.09
2.18
12.18
f1 (ppm)

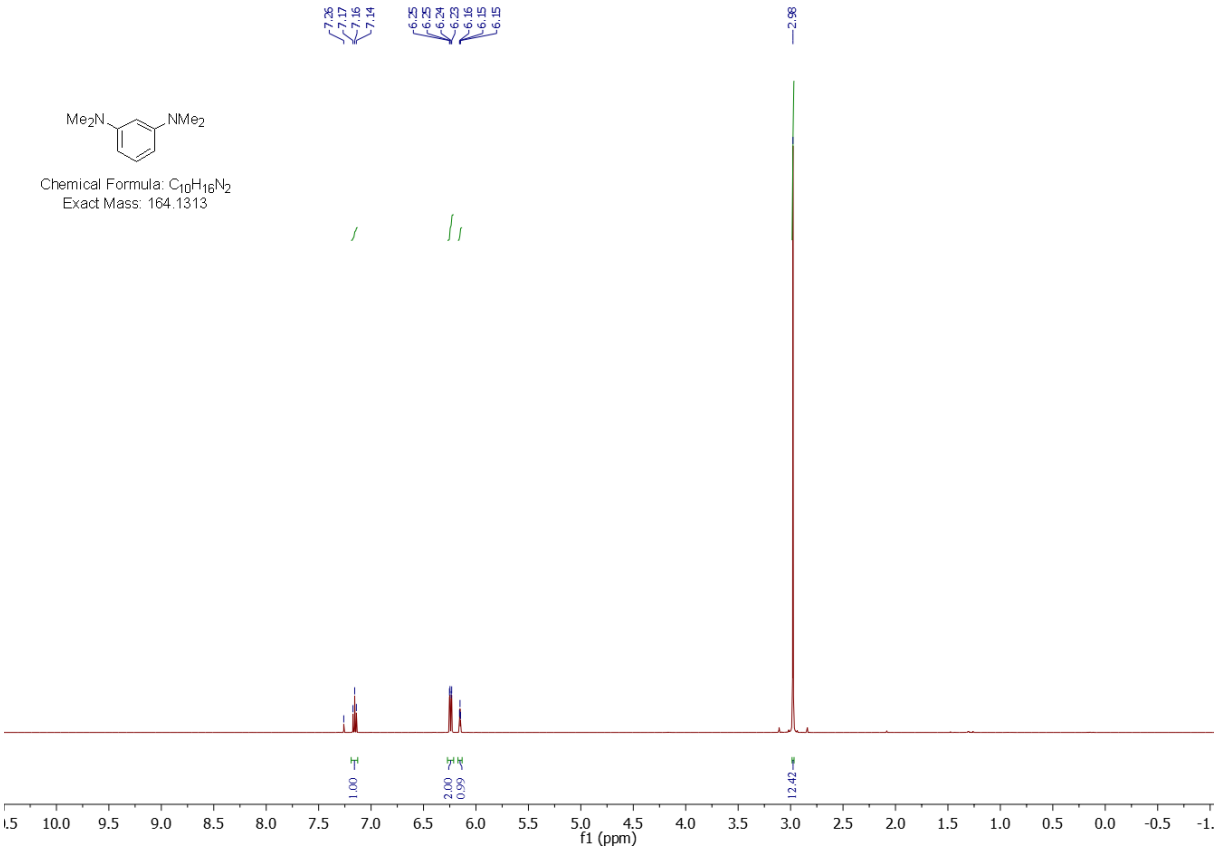

158.50
129.33
107.16
83.05
77.48
77.16
76.84
72.14
22.28
I
O
O
Chemical Formula: C12H17IO2
Exact Mass: 320.0273
f1 (ppm)

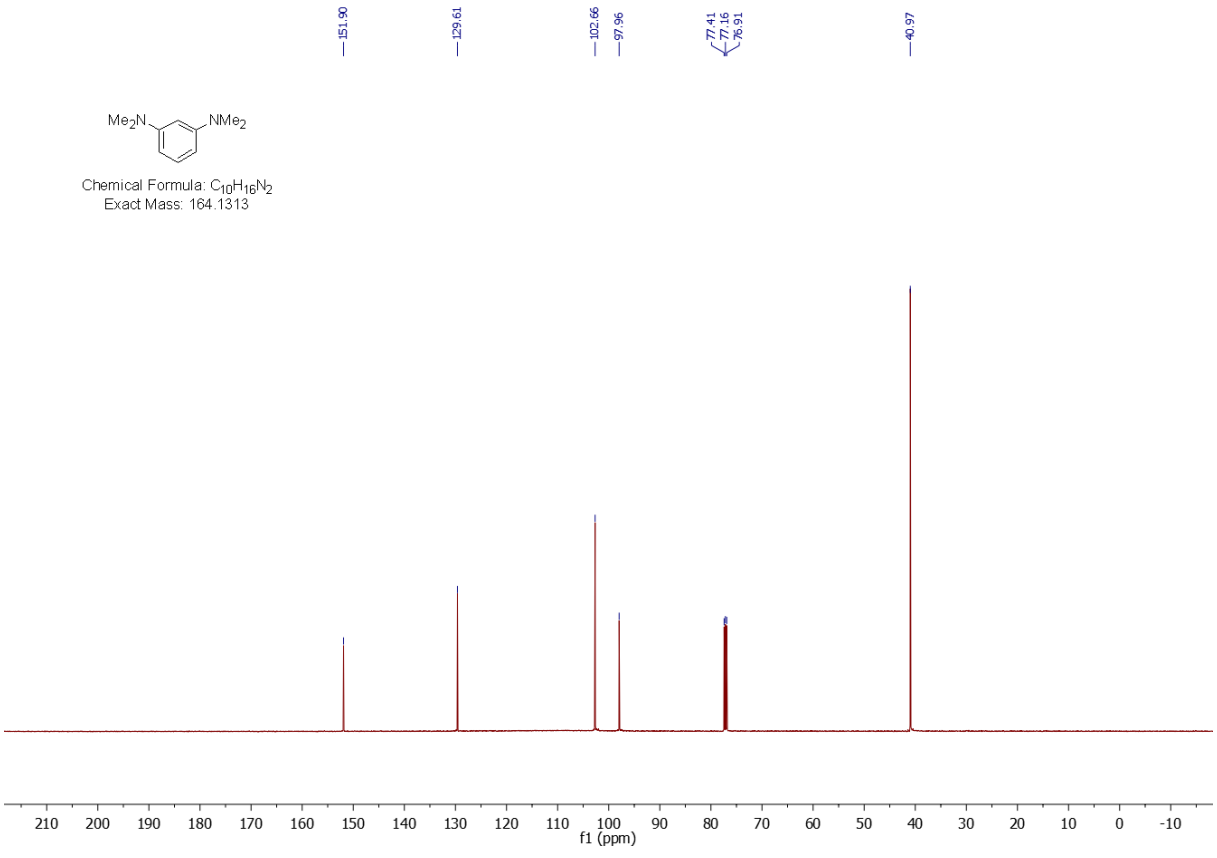

Chemical Formula: C18H26O2
Exact Mass: 274.1933
f1 (ppm)

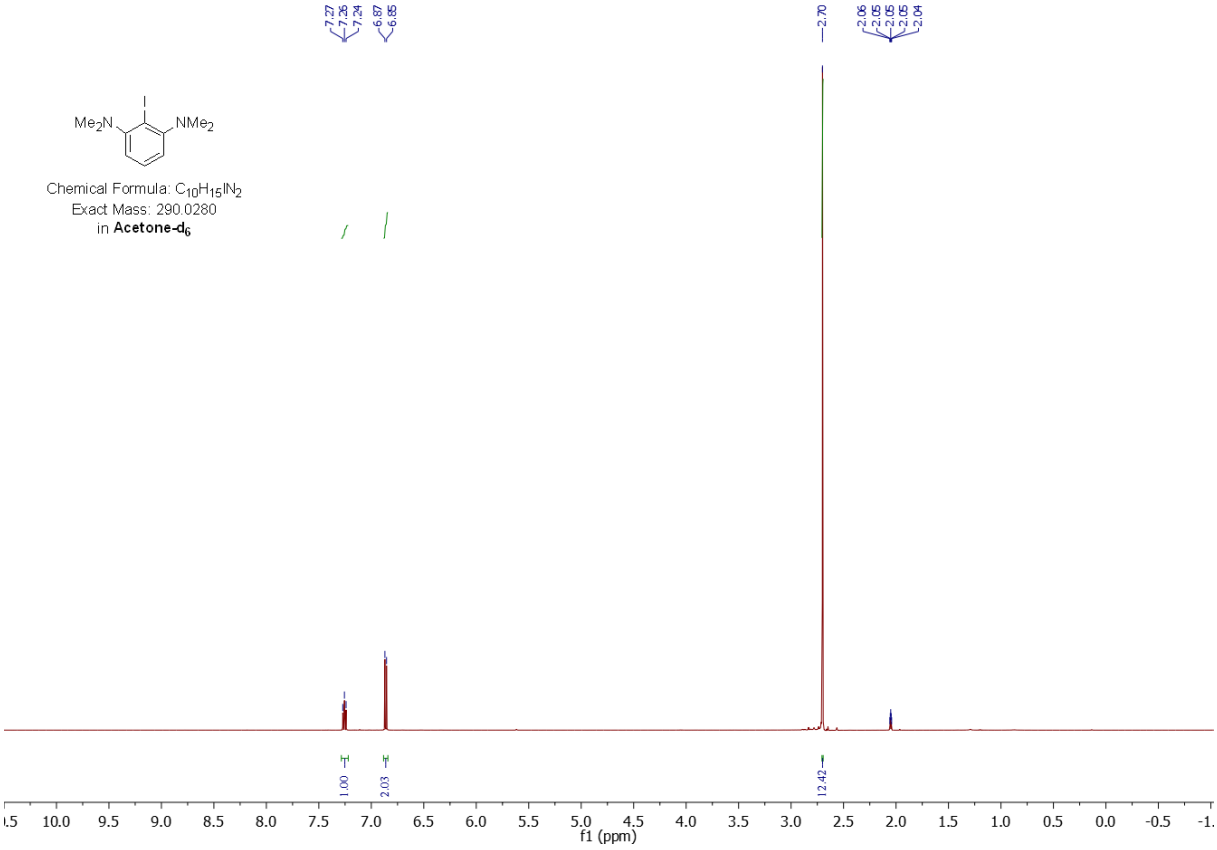

Chemical Formula: C18H26O2
Exact Mass: 274.1933
f1 (ppm)

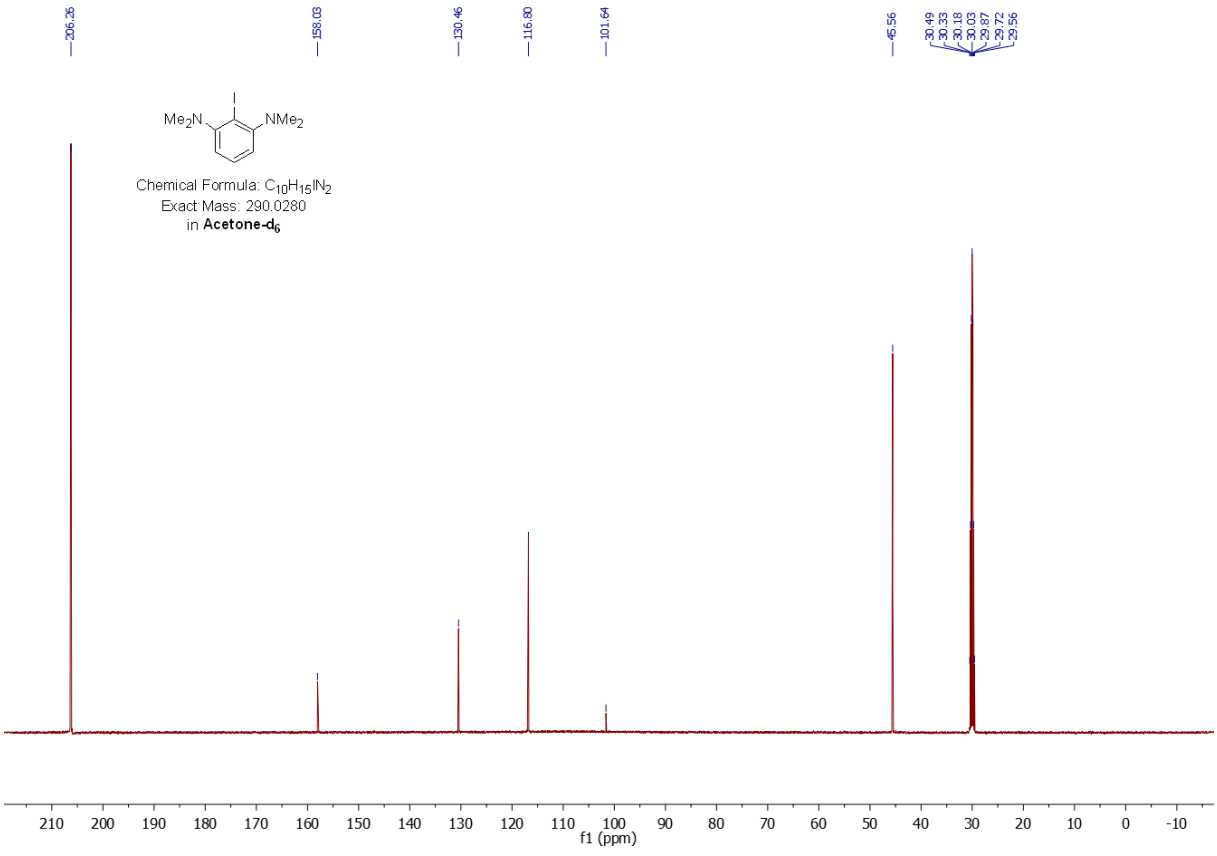

Chemical Formula: C18H25IO2
Exact Mass: 400.0899
f1 (ppm)

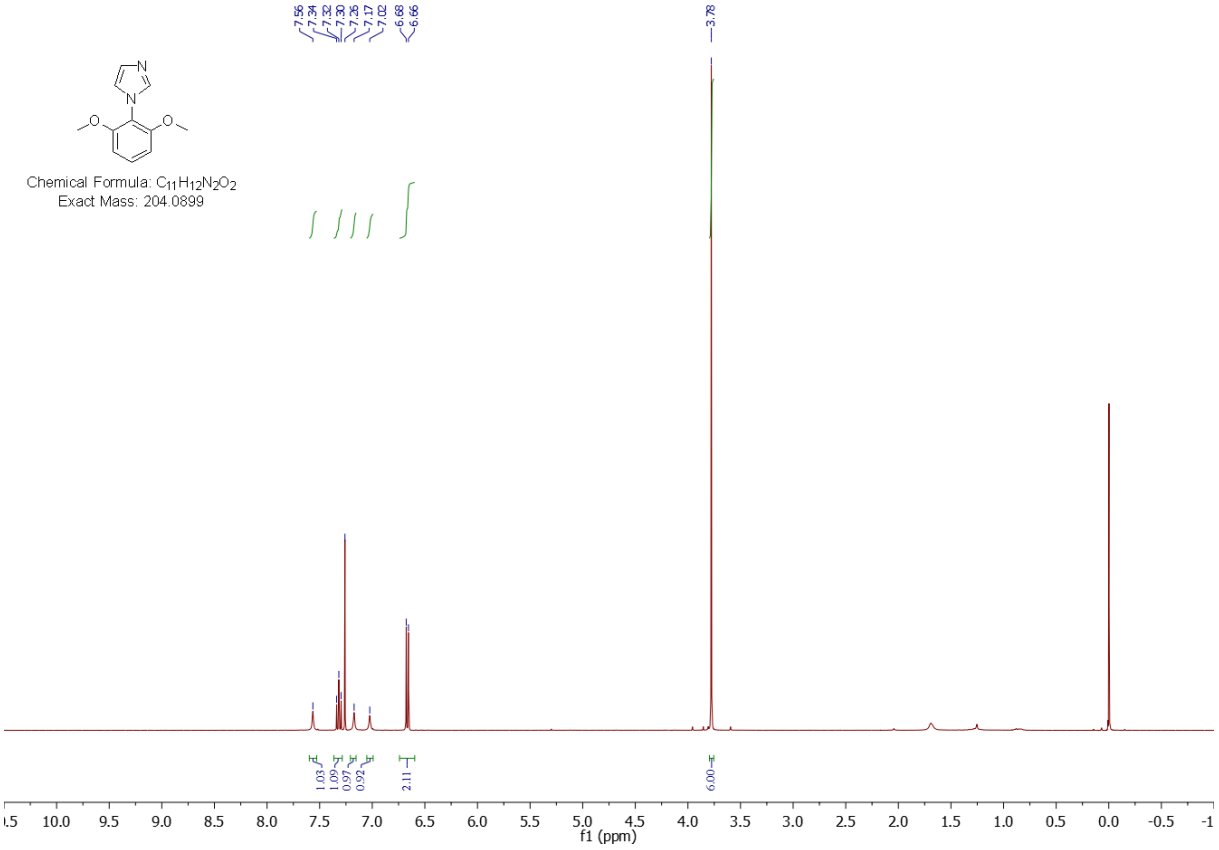

Chemical Formula: C18H25IO2
Exact Mass: 400.0899
f1 (ppm)

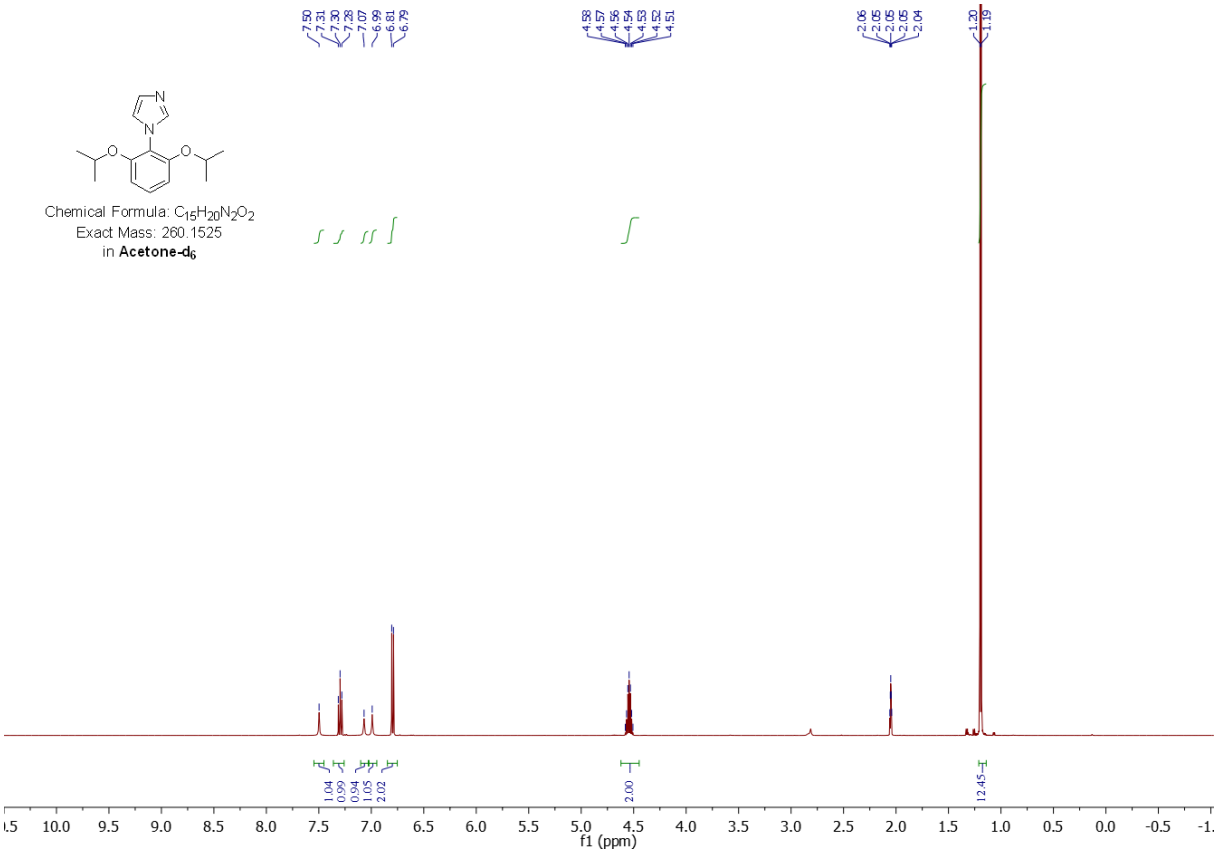

7.26
7.17
7.16
7.14
6.25
6.25
6.24
6.23
6.16
6.15
6.15
2.98
Me2N
NMe2
Chemical Formula: C10H16N2
Exact Mass: 164.1313
1.00
2.00
0.99
12.42
f1 (ppm)

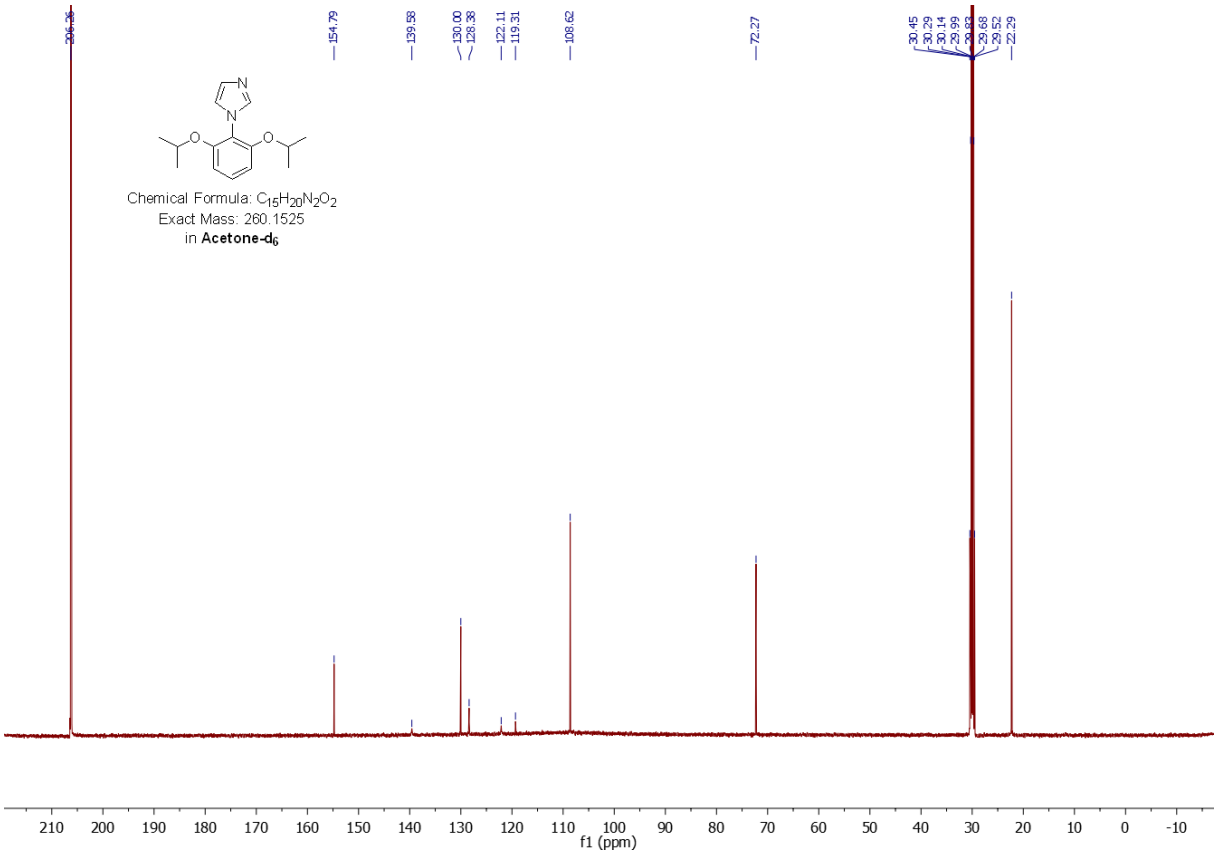

151.90
129.61
102.66
97.96
77.41
77.16
76.91
40.97
Me2N
NMe2
Chemical Formula: C10H16N2
Exact Mass: 164.1313
f1 (ppm)


7.27
7.26
7.24
6.87
6.85
2.70
2.06
2.05
2.05
2.05
2.04
Me2N
NMe2
Chemical Formula: C10H15IN2
Exact Mass: 290.0280
in Acetone-d6
1.00
2.03
12.42
f1 (ppm)


206.26
158.03
130.46
116.80
101.64
45.56
30.49
30.33
30.18
30.03
29.87
29.72
29.56
Me2N
NMe2
Chemical Formula: C10H15IN2
Exact Mass: 290.0280
in Acetone-d6
f1 (ppm)


Chemical Formula: C11H12N2O2
Exact Mass: 204.0899
f1 (ppm)


Chemical Formula: C15H20N2O2
Exact Mass: 260.1525
in Acetone-d6
f1 (ppm)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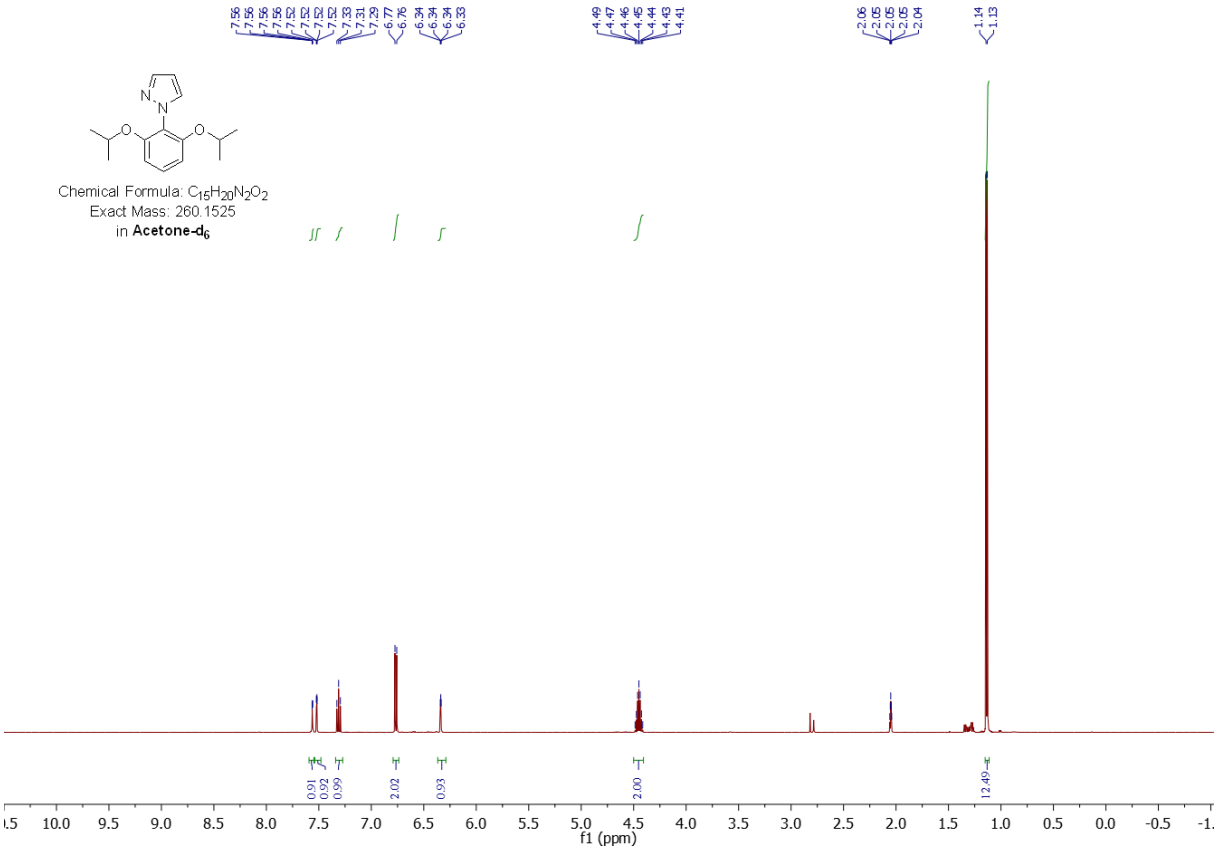
154.79
139.58
130.00
128.38
122.11
119.31
108.62
72.27
30.45
30.29
30.14
29.99
29.83
29.68
29.52
22.29
Chemical Formula: C15H20N2O2
Exact Mass: 260.1525
in Acetone-d6
f1 (ppm)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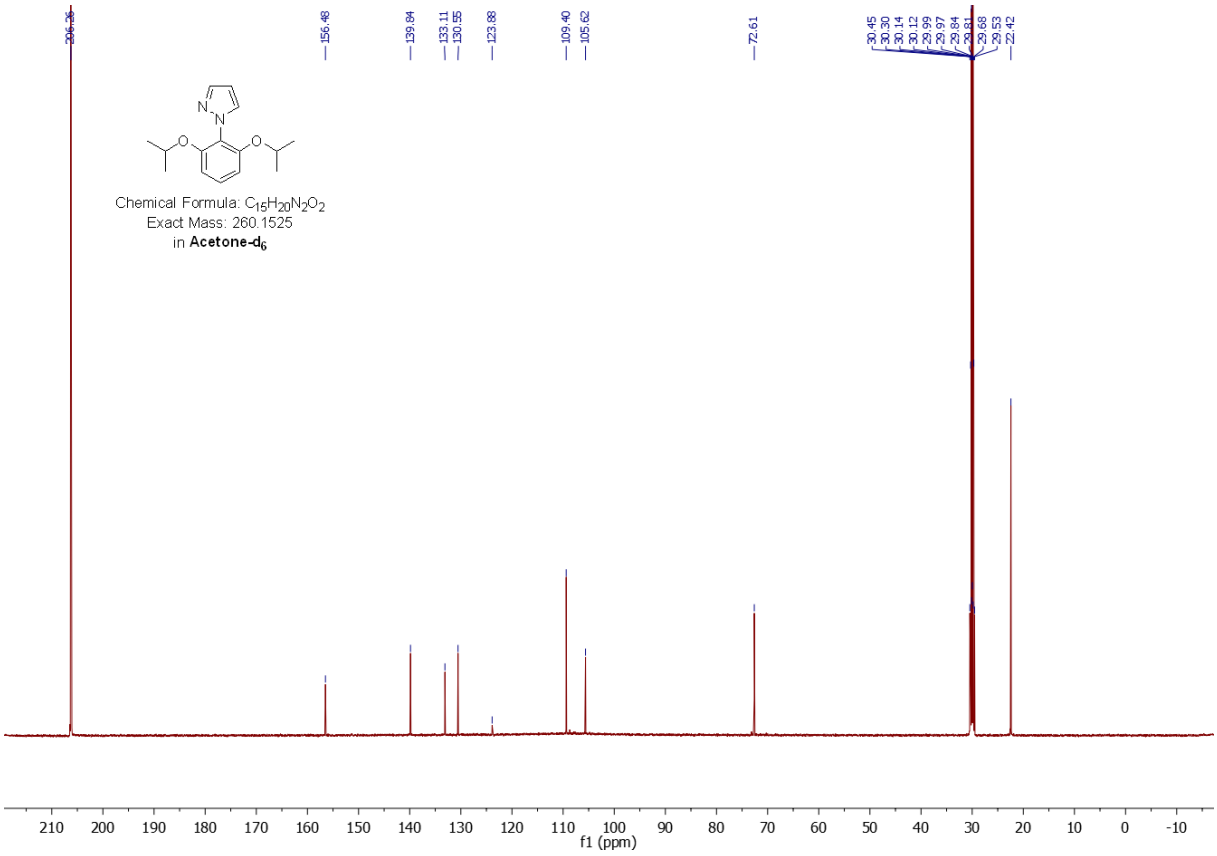
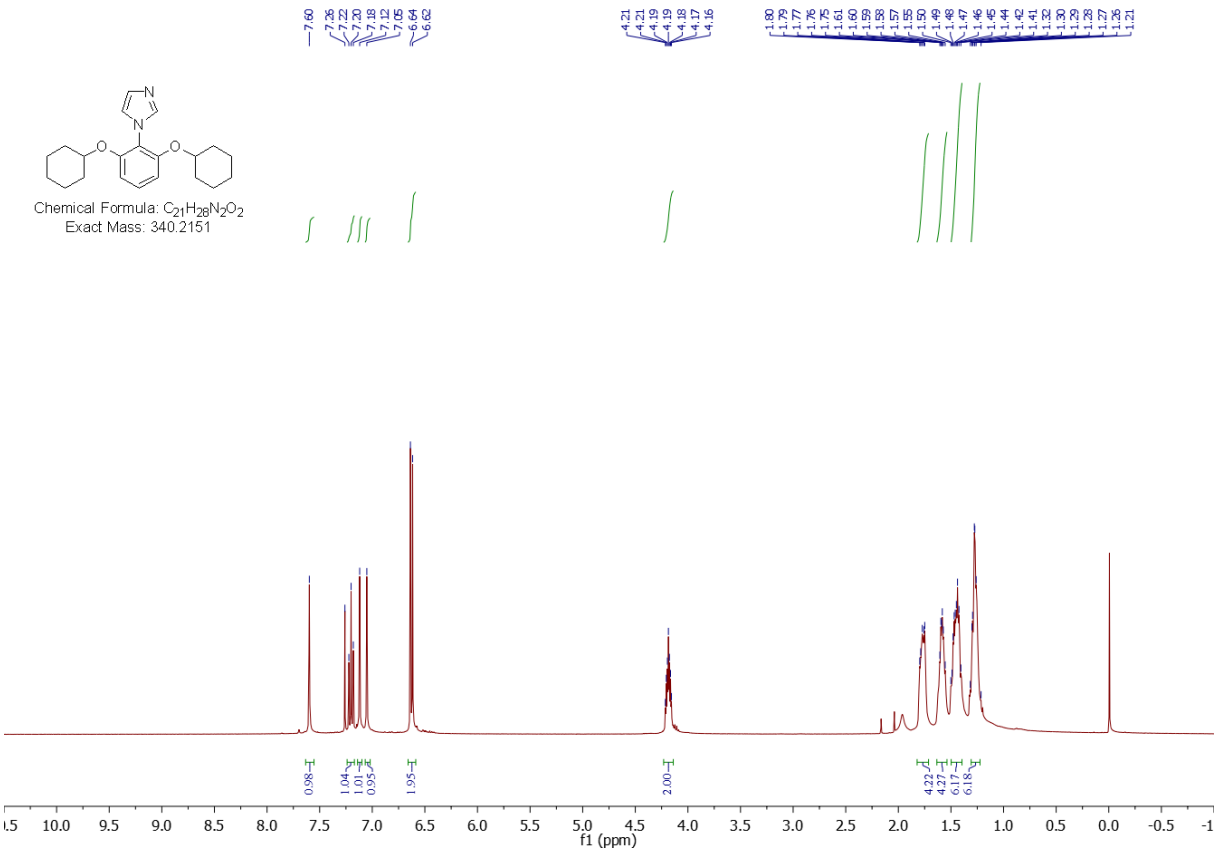
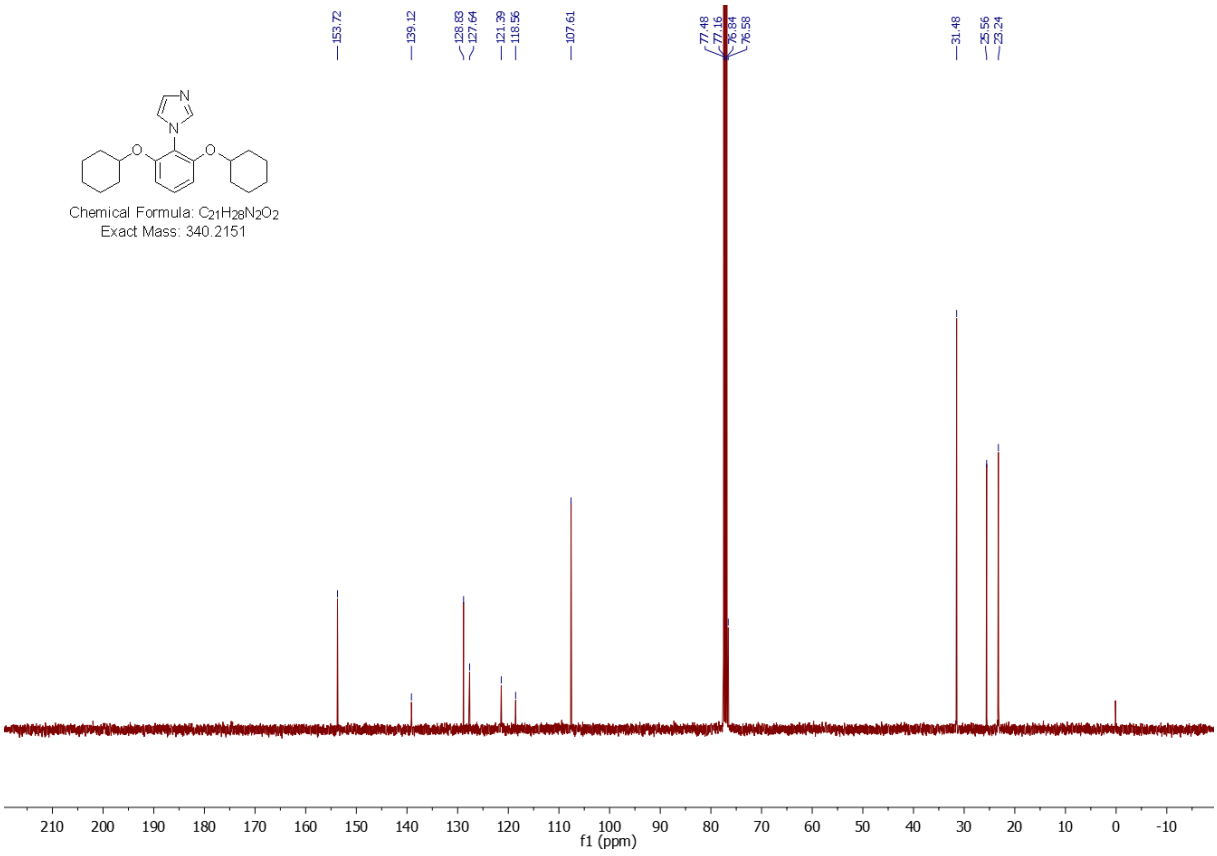
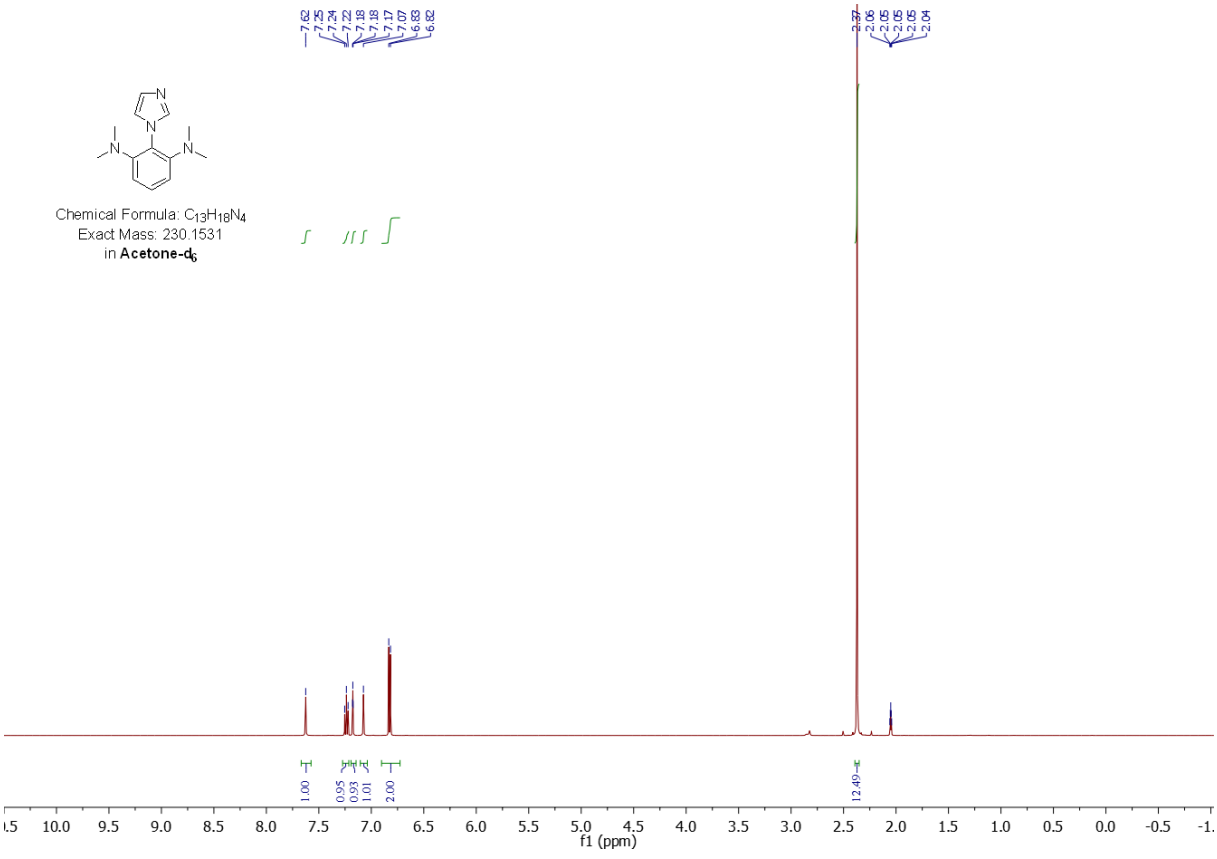
7.56
7.56
7.56
7.52
7.52
7.52
7.52
7.33
7.31
7.29
6.77
6.76
6.34
6.34
6.34
6.33
4.49
4.47
4.46
4.45
4.44
4.43
4.41
2.06
2.05
2.05
2.05
2.04
1.14
1.13
0.91
0.92
0.99
2.02
0.93
2.00
12.49
Chemical Formula: C15H20N2O2
Exact Mass: 260.1525
in Acetone-d6
f1 (ppm)


206.36
156.48
139.84
133.11
130.55
123.88
109.40
105.62
72.61
30.45
30.30
30.14
30.12
29.99
29.97
29.84
29.81
29.68
29.53
22.42
Chemical Formula: C15H20N2O2
Exact Mass: 260.1525
in Acetone-d6
f1 (ppm)


7.60
7.26
7.22
7.20
7.18
7.12
7.05
6.64
6.62
4.21
4.21
4.19
4.19
4.18
4.17
4.16
1.80
1.79
1.77
1.76
1.75
1.61
1.60
1.59
1.58
1.57
1.55
1.50
1.49
1.48
1.47
1.46
1.45
1.44
1.42
1.41
1.32
1.30
1.29
1.28
1.27
1.26
1.21
Chemical Formula: C21H28N2O2
Exact Mass: 340.2151
0.98
1.04
1.01
0.95
1.95
2.00
4.22
4.27
6.17
6.18
f1 (ppm)


153.72
139.12
128.83
127.64
121.39
118.56
107.61
77.48
77.16
76.84
76.58
31.48
25.56
23.24
Chemical Formula: C21H28N2O2
Exact Mass: 340.2151
f1 (ppm)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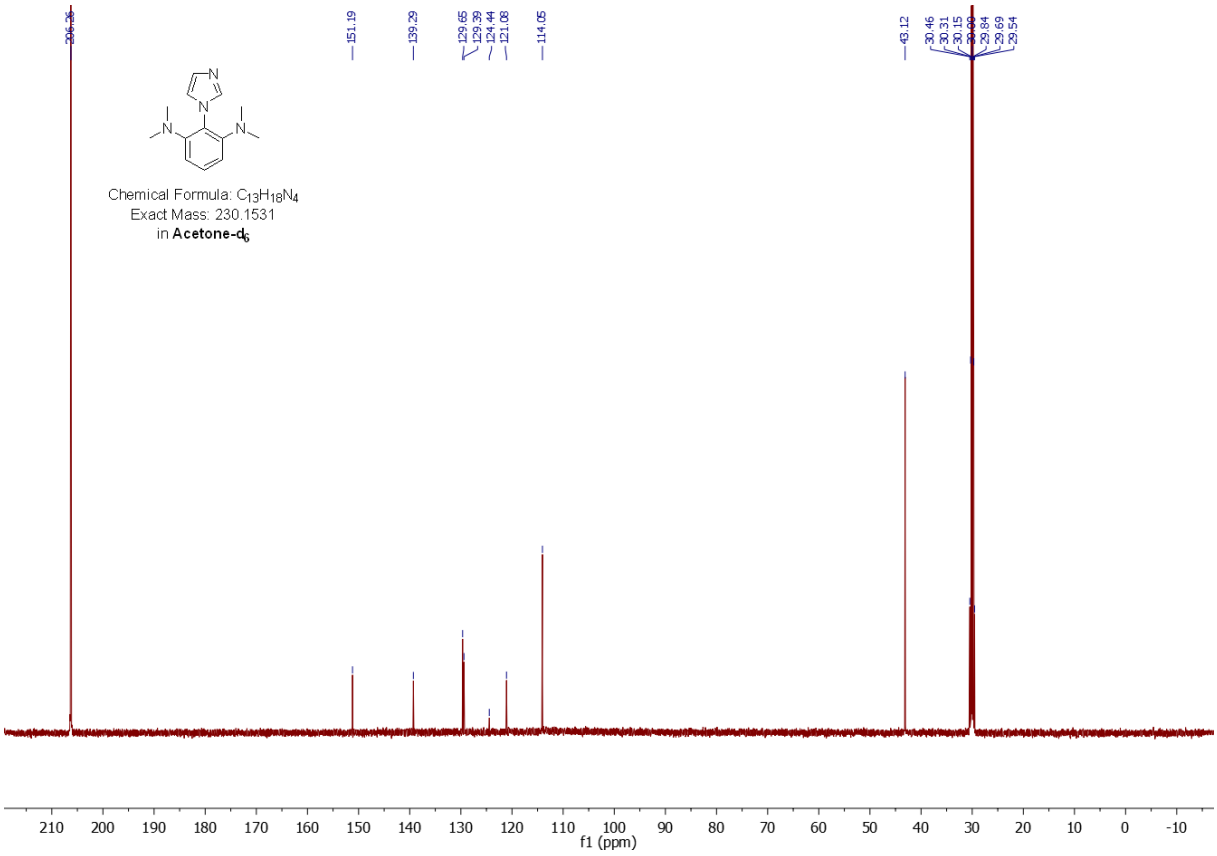
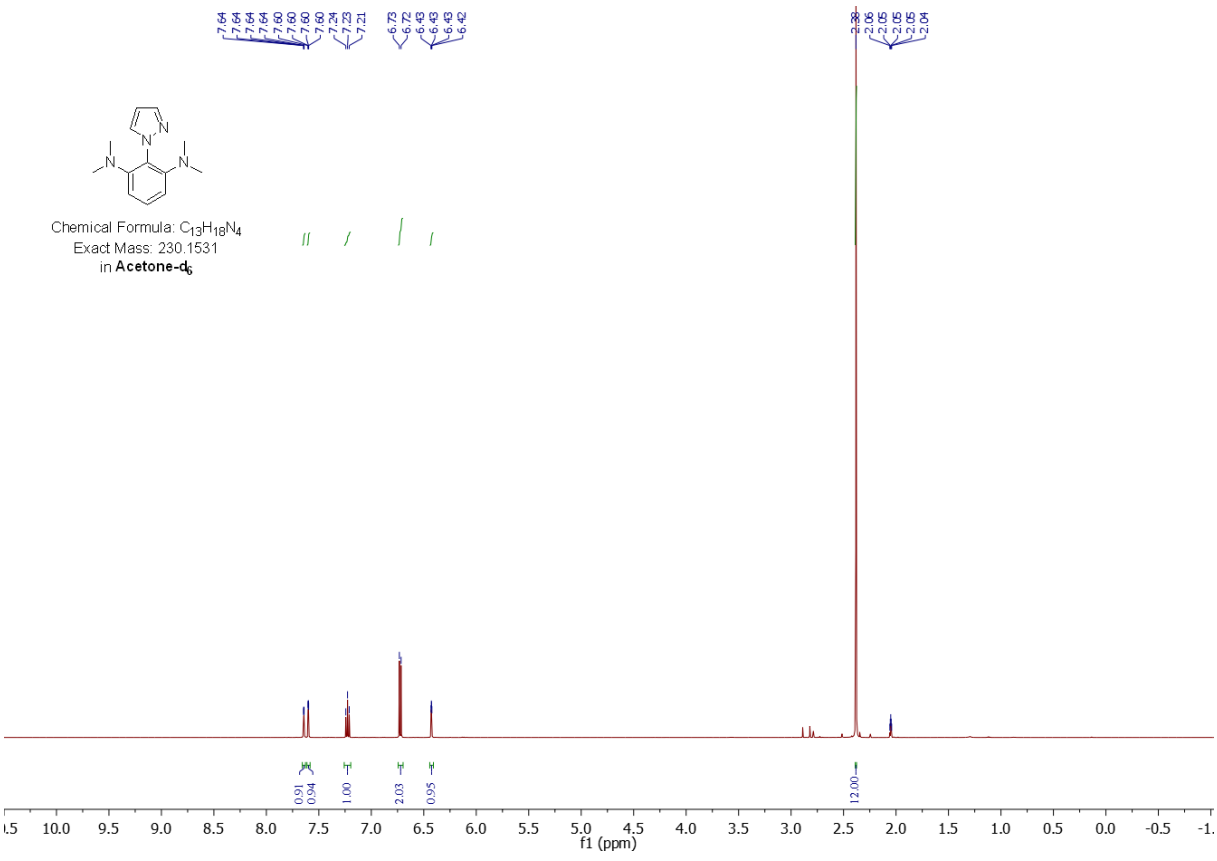
7.25
7.24
7.22
7.18
7.17
7.07
6.83
6.82
2.87
2.06
2.05
2.05
2.05
2.04
Chemical Formula: C13H18N4
Exact Mass: 230.1531
in Acetone-d6
1.00
0.95
0.93
1.01
2.00
12.49
f1 (ppm)


206.26
151.19
139.29
129.65
129.39
124.44
121.08
114.05
43.12
30.46
30.31
30.15
29.84
29.69
29.54
Chemical Formula: C13H18N4
Exact Mass: 230.1531
in Acetone-d6
f1 (ppm)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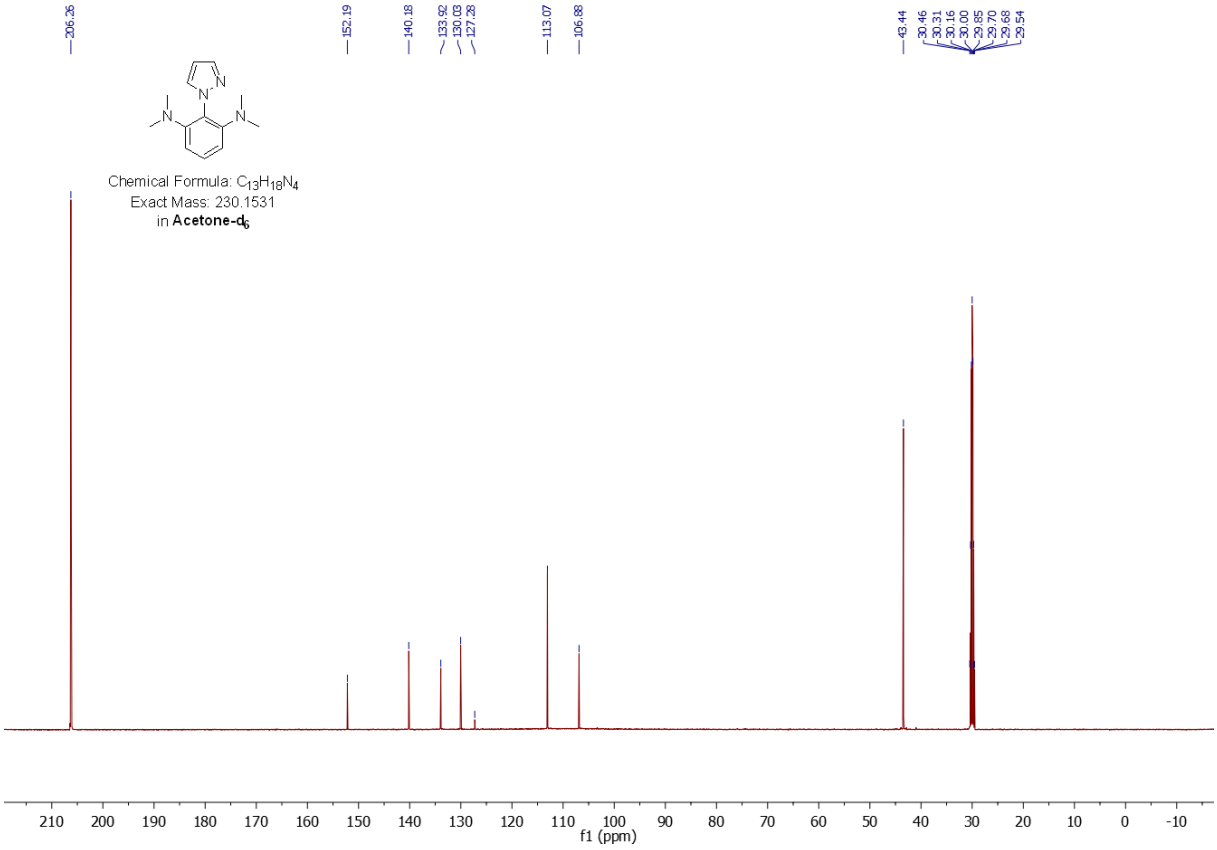
7.64
7.64
7.64
7.60
7.60
7.60
7.60
7.24
7.23
7.21
6.73
6.72
6.43
6.43
6.43
6.42
2.38
2.06
2.05
2.05
2.05
2.04
0.91
0.94
1.00
2.03
0.95
12.00
Chemical Formula: C13H18N4
Exact Mass: 230.1531
in Acetone-d6
f1 (ppm)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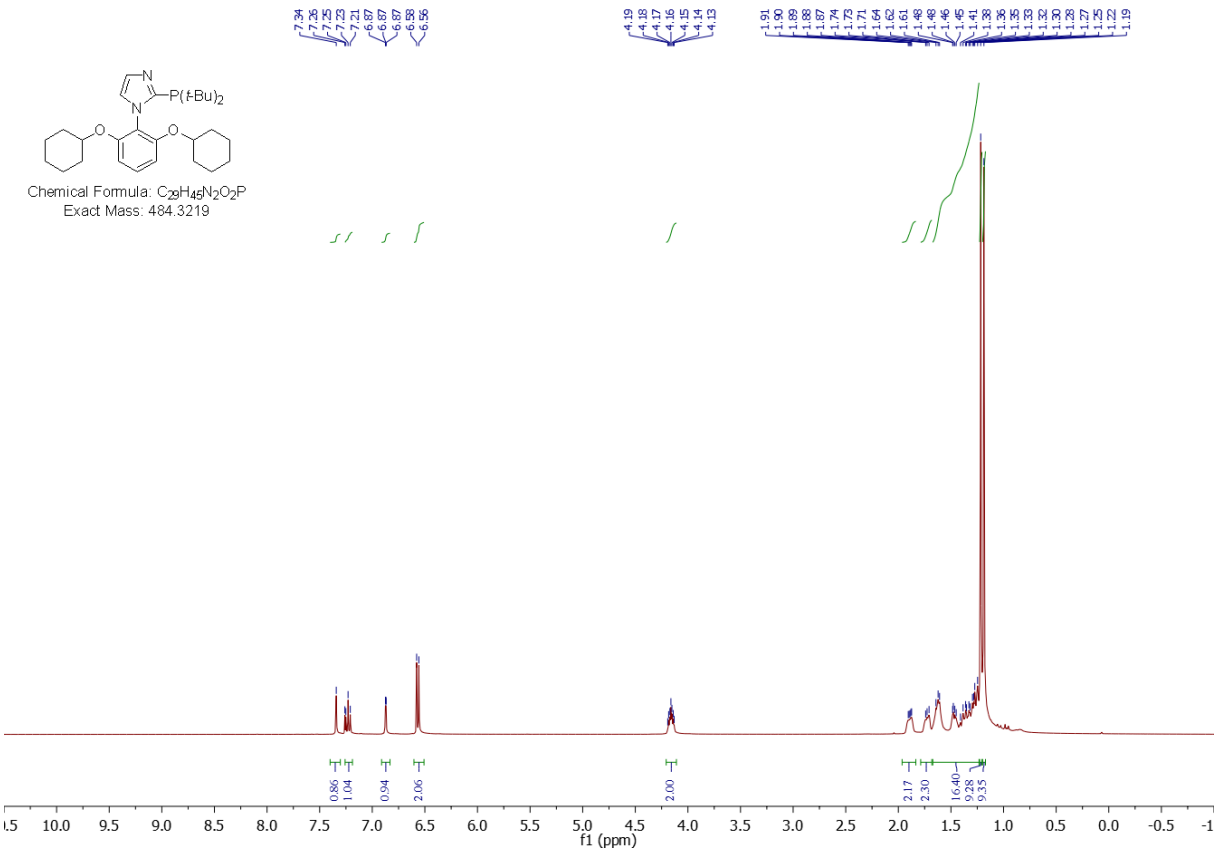
152.19
140.18
133.92
130.03
127.28
113.07
106.88
43.44
30.46
30.31
30.16
30.00
29.85
29.70
29.68
29.54
Chemical Formula: C13H18N4
Exact Mass: 230.1531
in Acetone-d6
f1 (ppm)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7.21
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6.87
6.58
6.56
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4.18
4.17
4.16
4.15
4.14
4.13
1.91
1.90
1.89
1.88
1.87
1.74
1.73
1.71
1.64
1.62
1.61
1.48
1.46
1.45
1.41
1.38
1.36
1.35
1.33
1.32
1.30
1.28
1.27
1.25
1.22
1.19
P(t-Bu)2
Chemical Formula: C29H45N2O2P
Exact Mass: 484.3219
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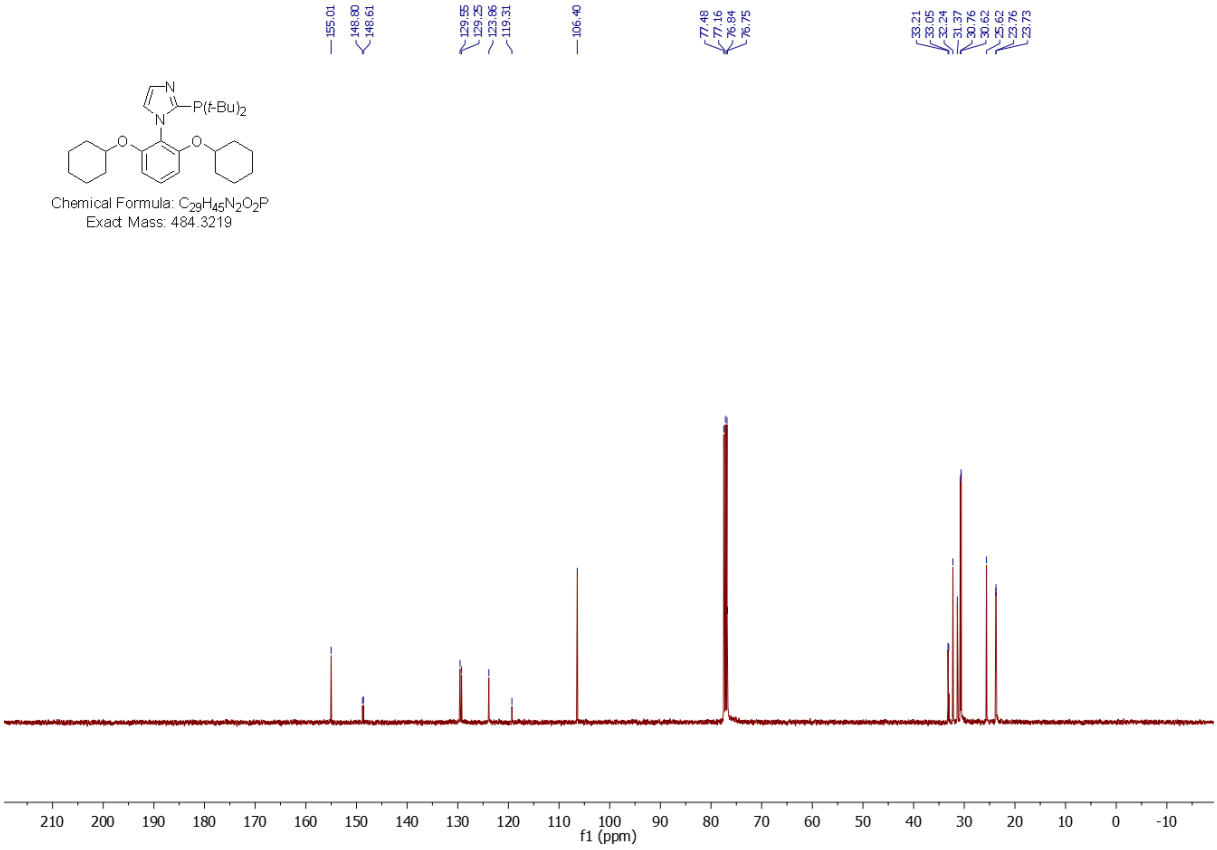
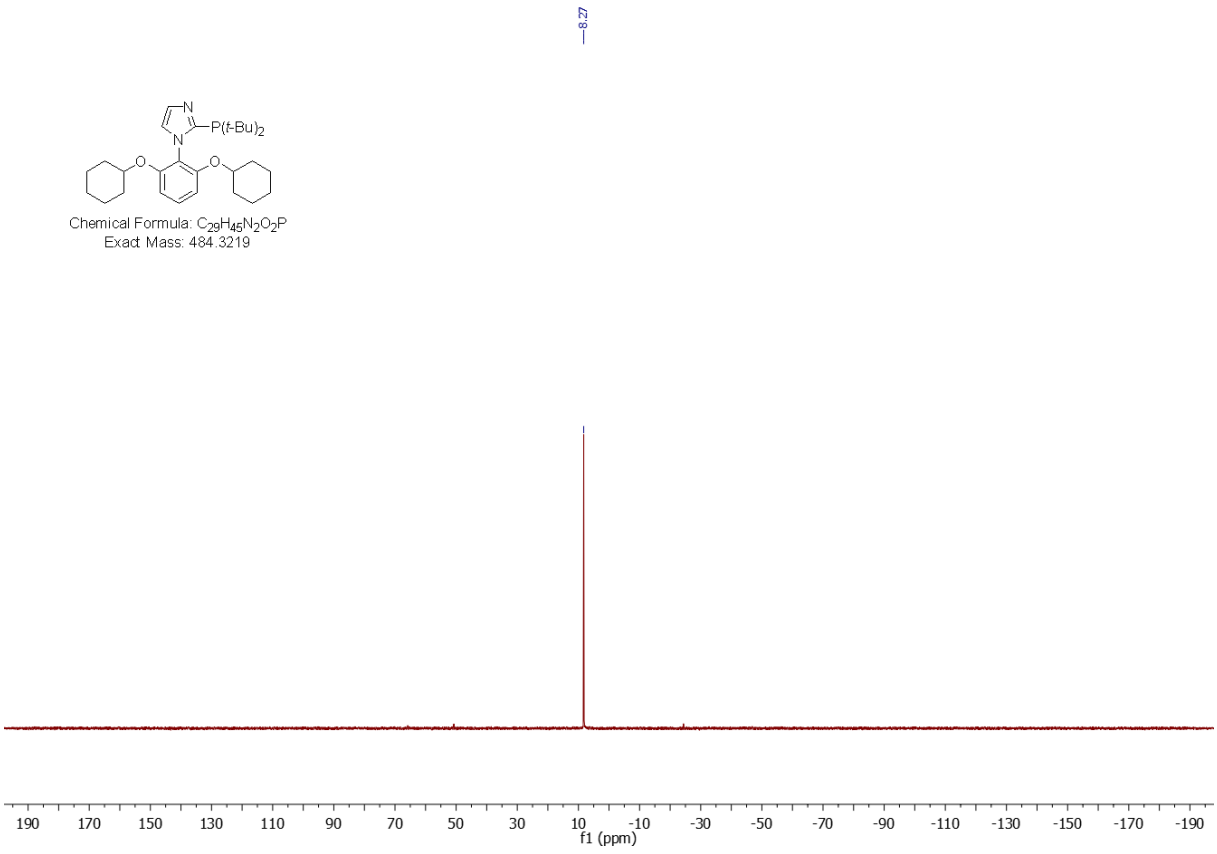
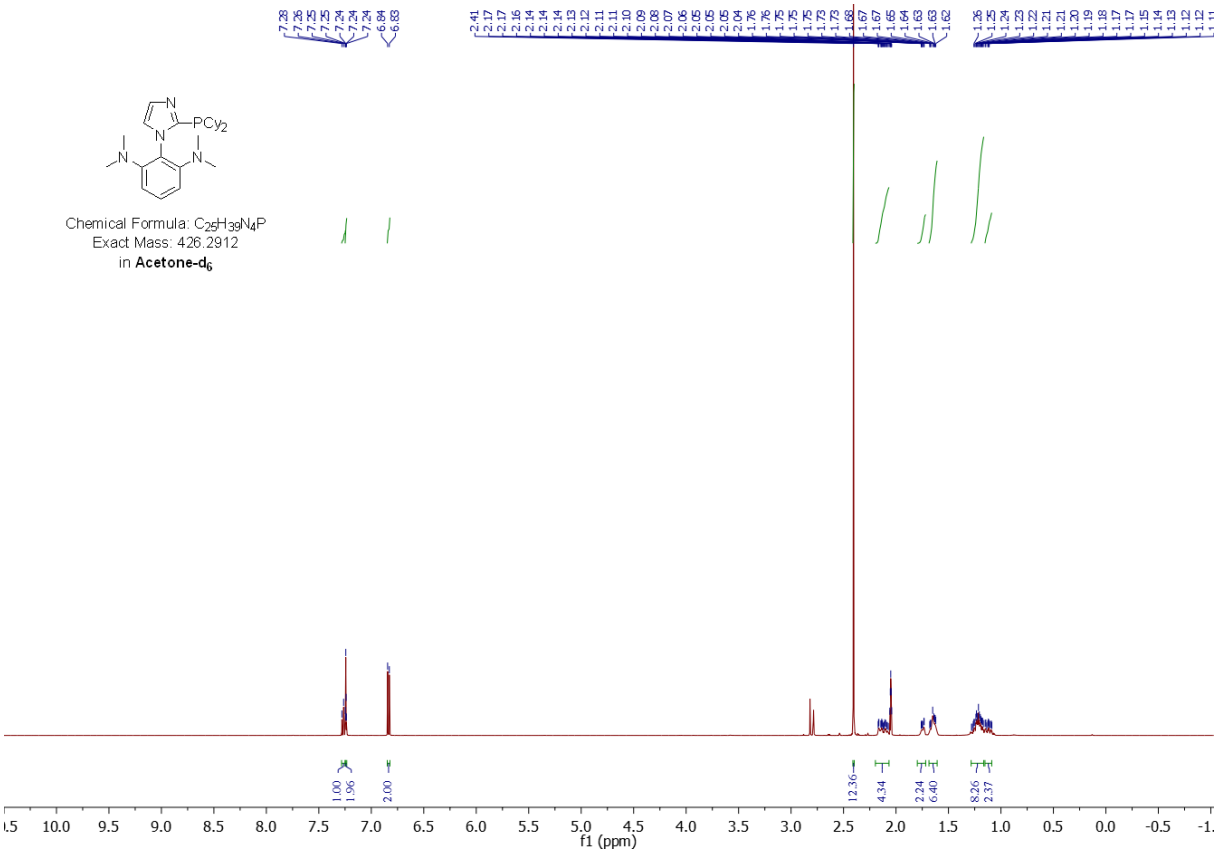
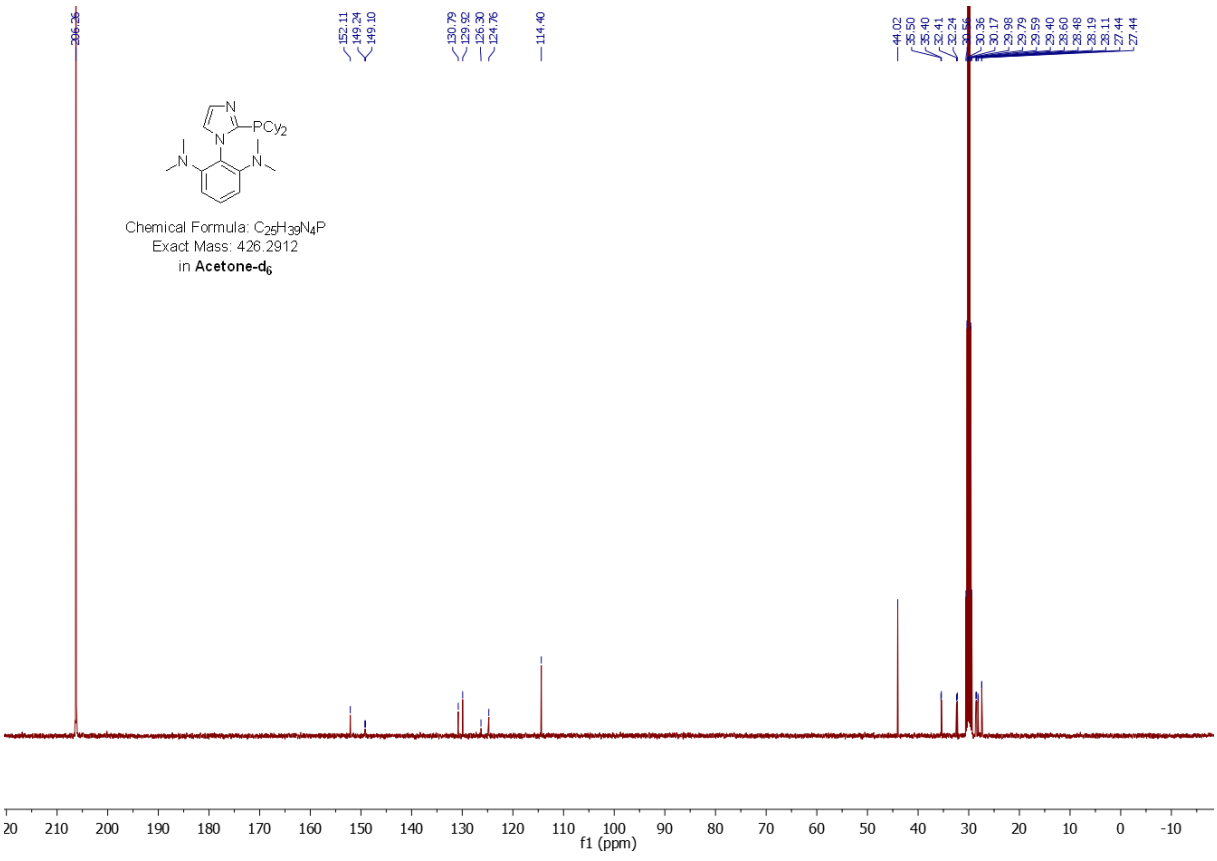
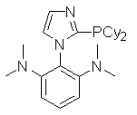
1.04
0.94
2.06
2.00
2.17
2.30
16.40
9.28
9.35
f1 (ppm)


155.01
148.80
148.61
129.55
129.25
123.86
119.31
106.40
77.48
77.16
76.84
76.75
33.21
33.05
32.24
31.37
30.76
30.62
25.62
23.76
23.73
P(t-Bu)2
Chemical Formula: C29H45N2O2P
Exact Mass: 484.3219
f1 (ppm)

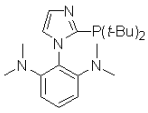

8.27
P(t-Bu)2
Chemical Formula: C29H45N2O2P
Exact Mass: 484.3219
f1 (ppm)


Chemical Formula: C25H39N4P
Exact Mass: 426.2912
in Acetone-d6
f1 (ppm)

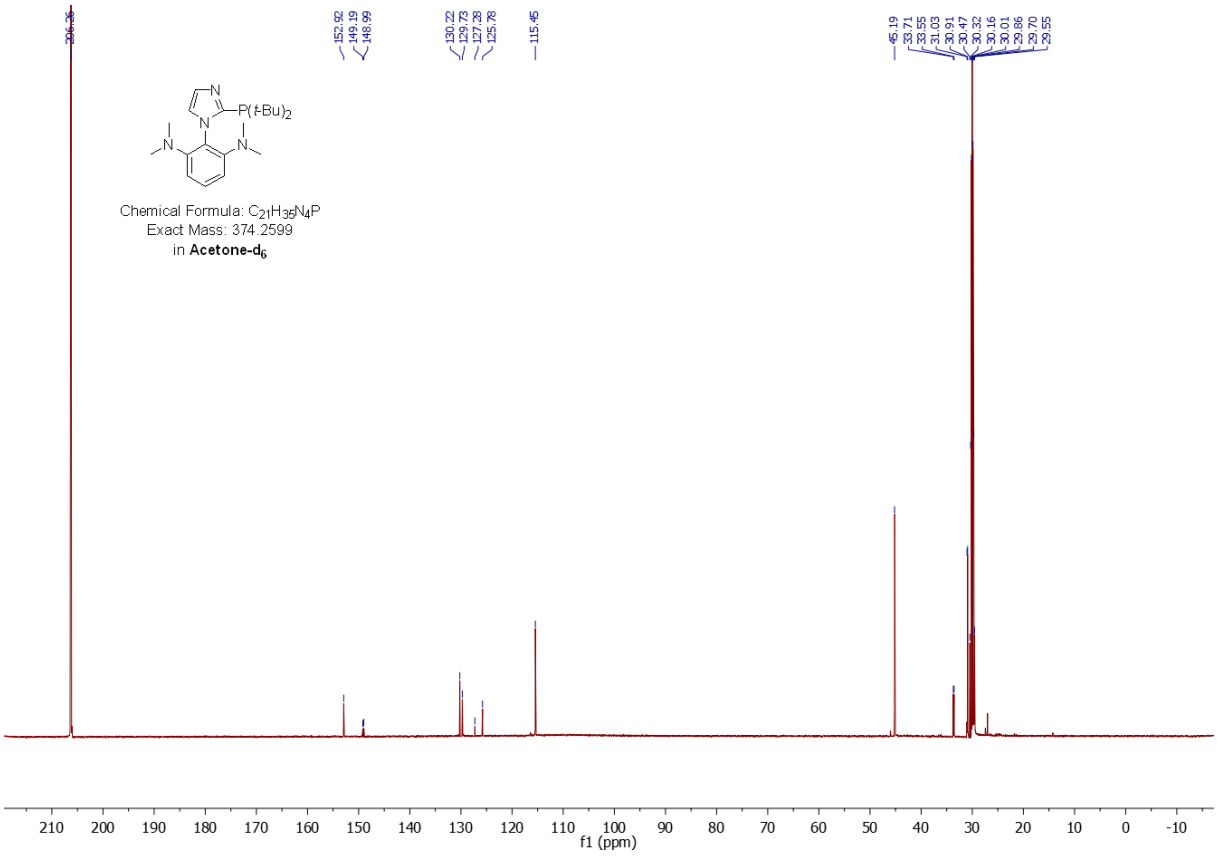

Chemical Formula: C25H39N4P
Exact Mass: 426.2912
in Acetone-d6
f1 (ppm)

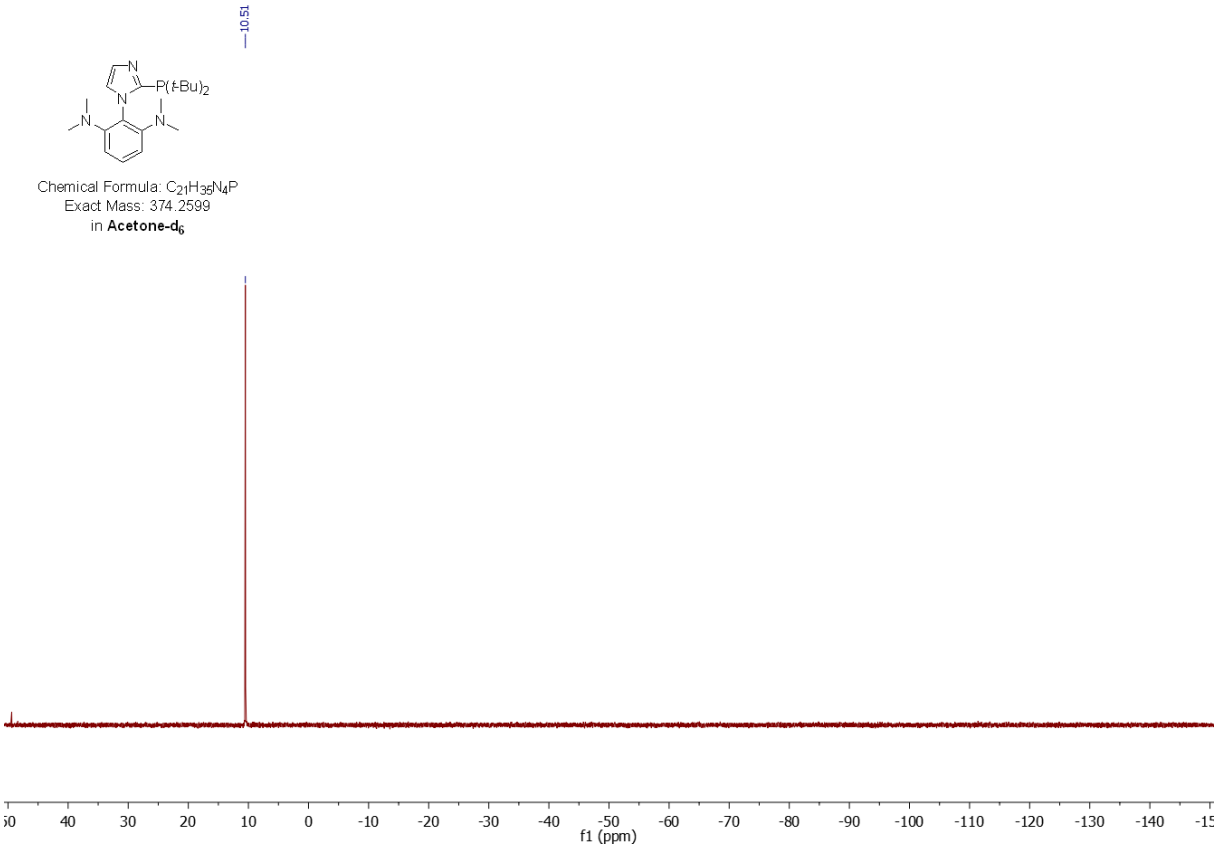


Chemical Formula: $C_{25}H_{39}N_4P$
Exact Mass: 426.2912
in **Acetone-d_6**



Chemical Formula: $C_{21}H_{35}N_4P$
Exact Mass: 374.2599
in **Acetone-d_6**


206.36
152.92
149.19
148.99
130.22
129.73
127.28
125.78
115.45
65.19
33.71
33.55
31.03
30.91
30.47
30.32
30.16
30.01
29.86
29.70
29.55
P(t-Bu)2
Chemical Formula: C21H36N4P
Exact Mass: 374.2599
in Acetone-d6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)


10.51
P(t-Bu)2
Chemical Formula: C21H36N4P
Exact Mass: 374.2599
in Acetone-d6
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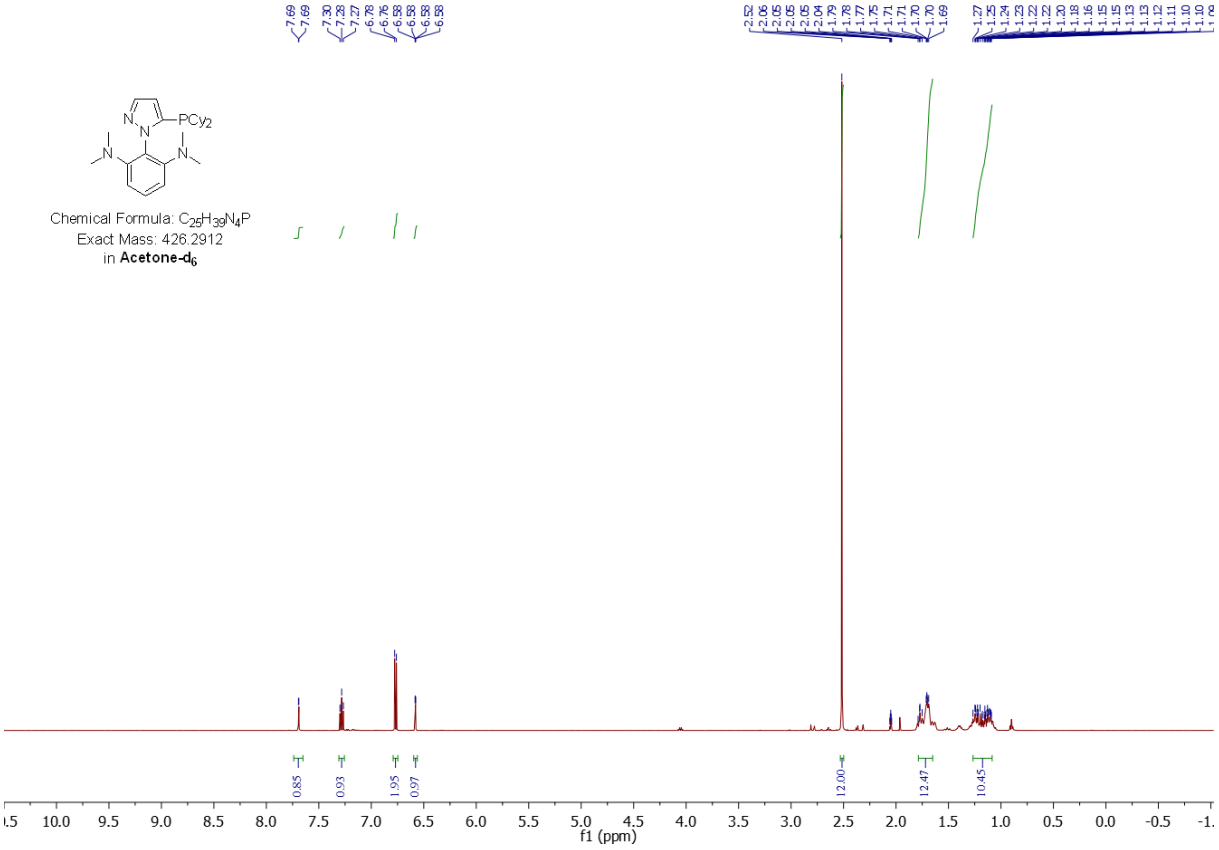
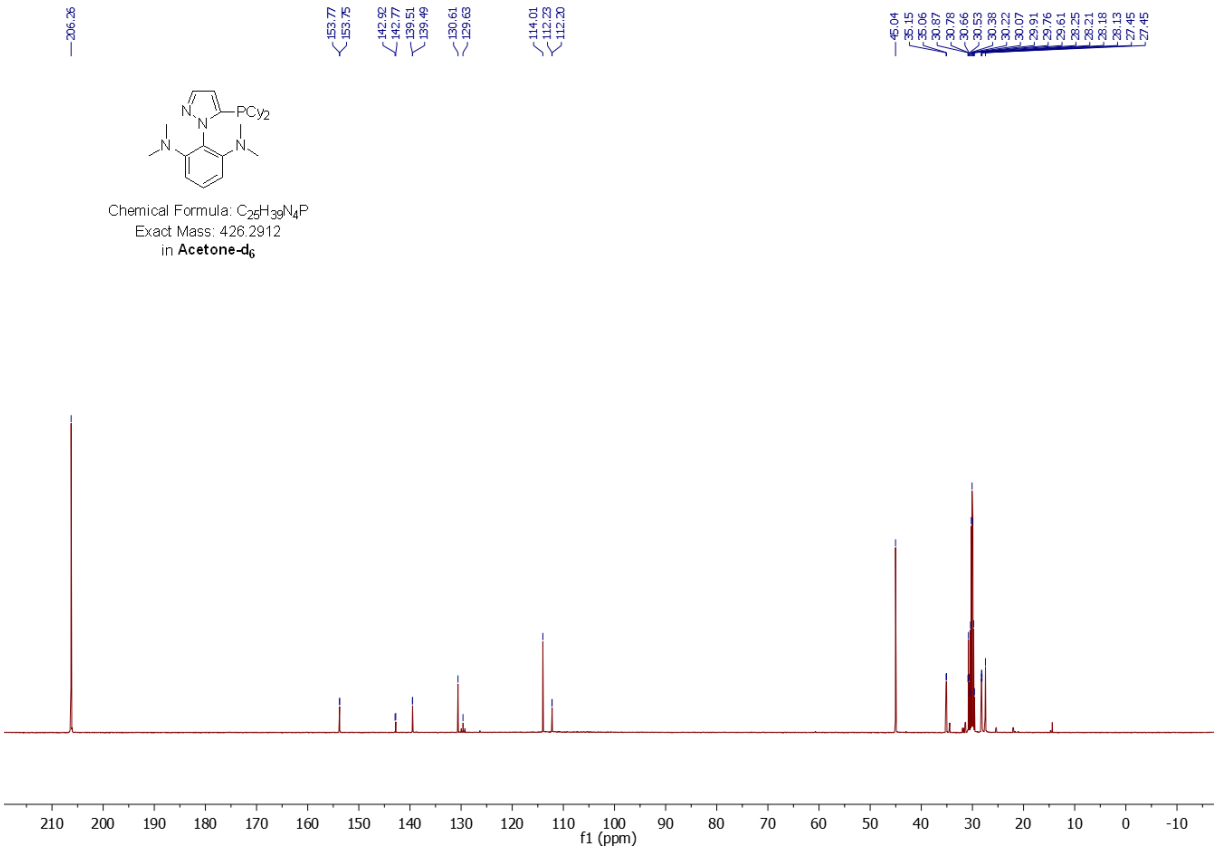
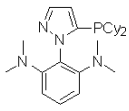
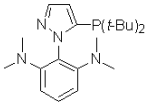
f1 (ppm)


PCy2
Chemical Formula: C25H39N4P
Exact Mass: 426.2912
in Acetone-d6
f1 (ppm)

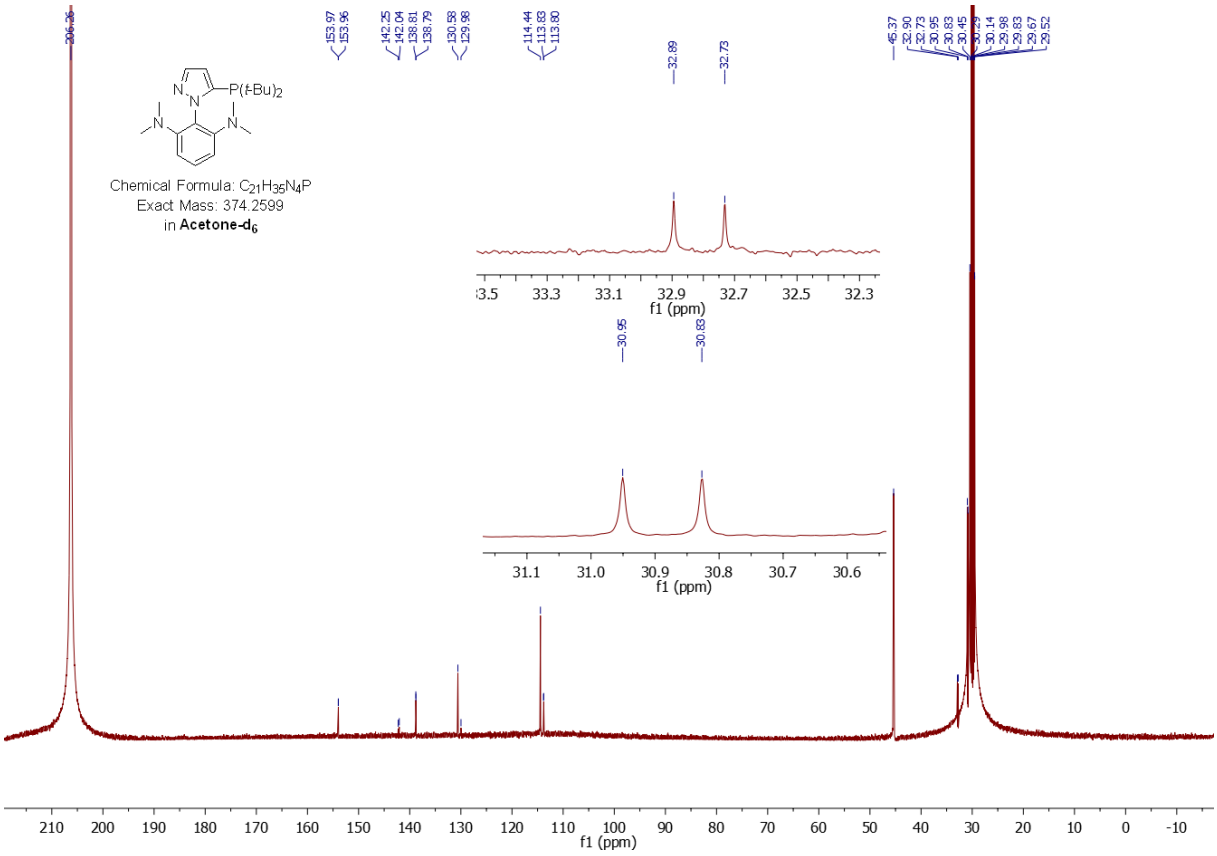

PCy2
Chemical Formula: C25H39N4P
Exact Mass: 426.2912
in Acetone-d6
f1 (ppm)

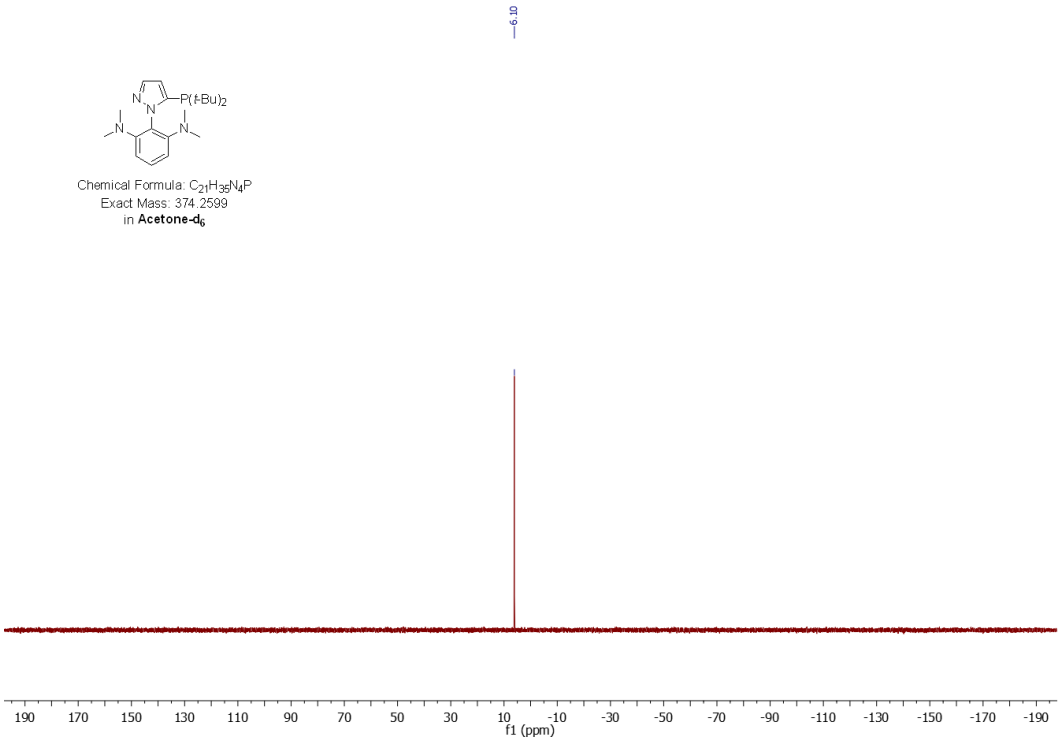


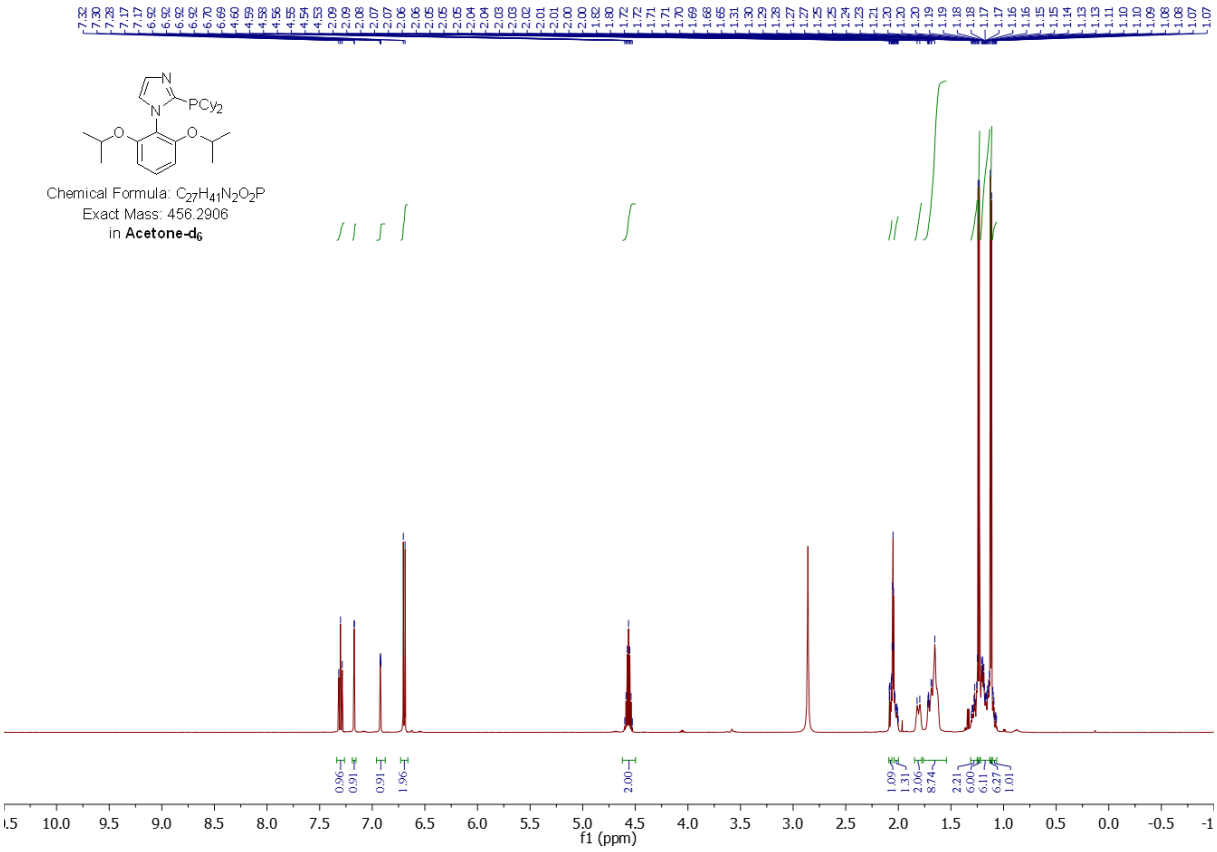
Chemical Formula: $C_{25}H_{39}N_4P$
Exact Mass: 426.2912
in **Acetone-d_6**

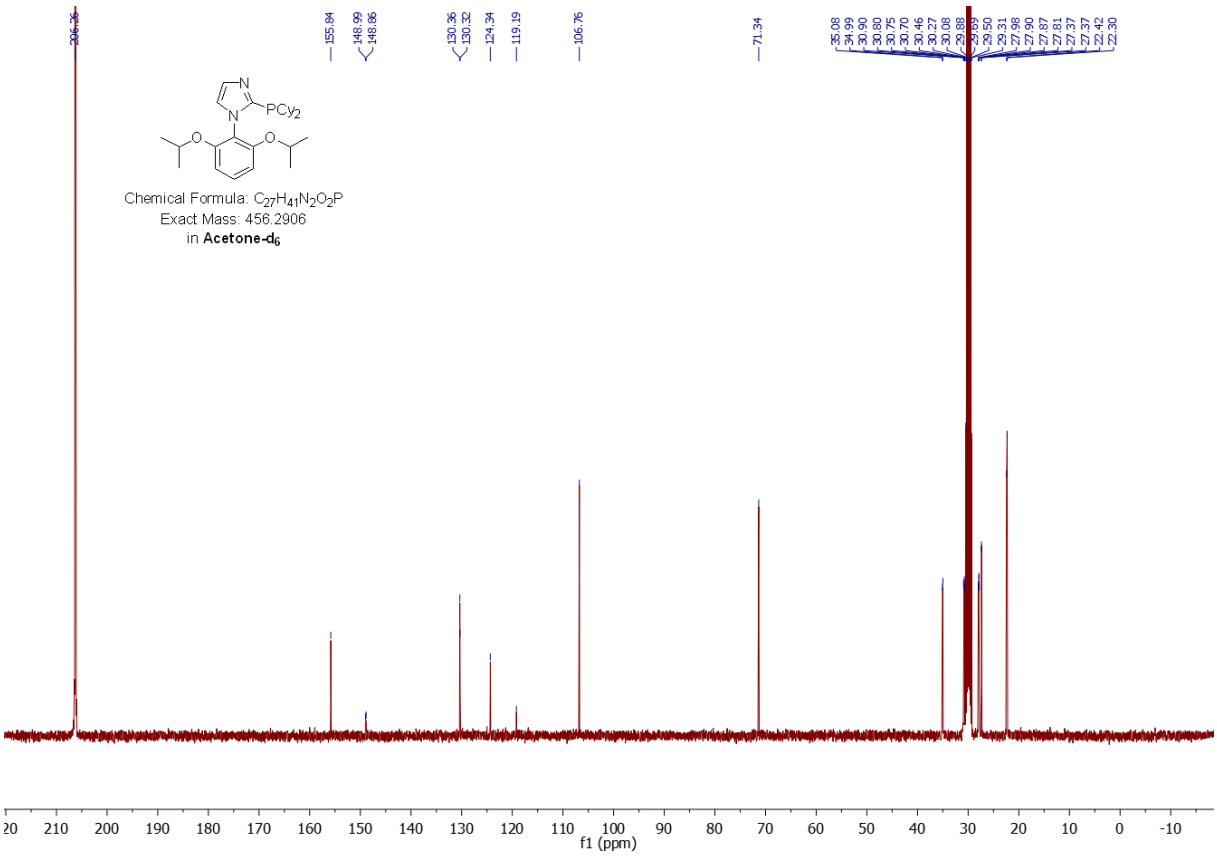


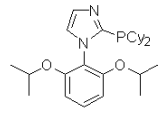
Chemical Formula: $C_{21}H_{35}N_4P$
Exact Mass: 374.2599
in **Acetone-d_6**


206.36
153.97
153.96
142.25
142.04
138.81
138.79
130.58
129.98
114.44
113.83
113.80
65.37
32.90
32.73
30.95
30.83
30.45
30.14
29.98
29.83
29.67
29.52
32.89
32.73
30.95
30.83
P(t-Bu)2
Chemical Formula: C21H35N4P
Exact Mass: 374.2599
in Acetone-d6
f1 (ppm)

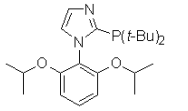

6.10
P(t-Bu)2
Chemical Formula: C21H35N4P
Exact Mass: 374.2599
in Acetone-d6
f1 (ppm)


PCy2
Chemical Formula: C27H41N2O2P
Exact Mass: 456.2906
in Acetone-d6
f1 (ppm)

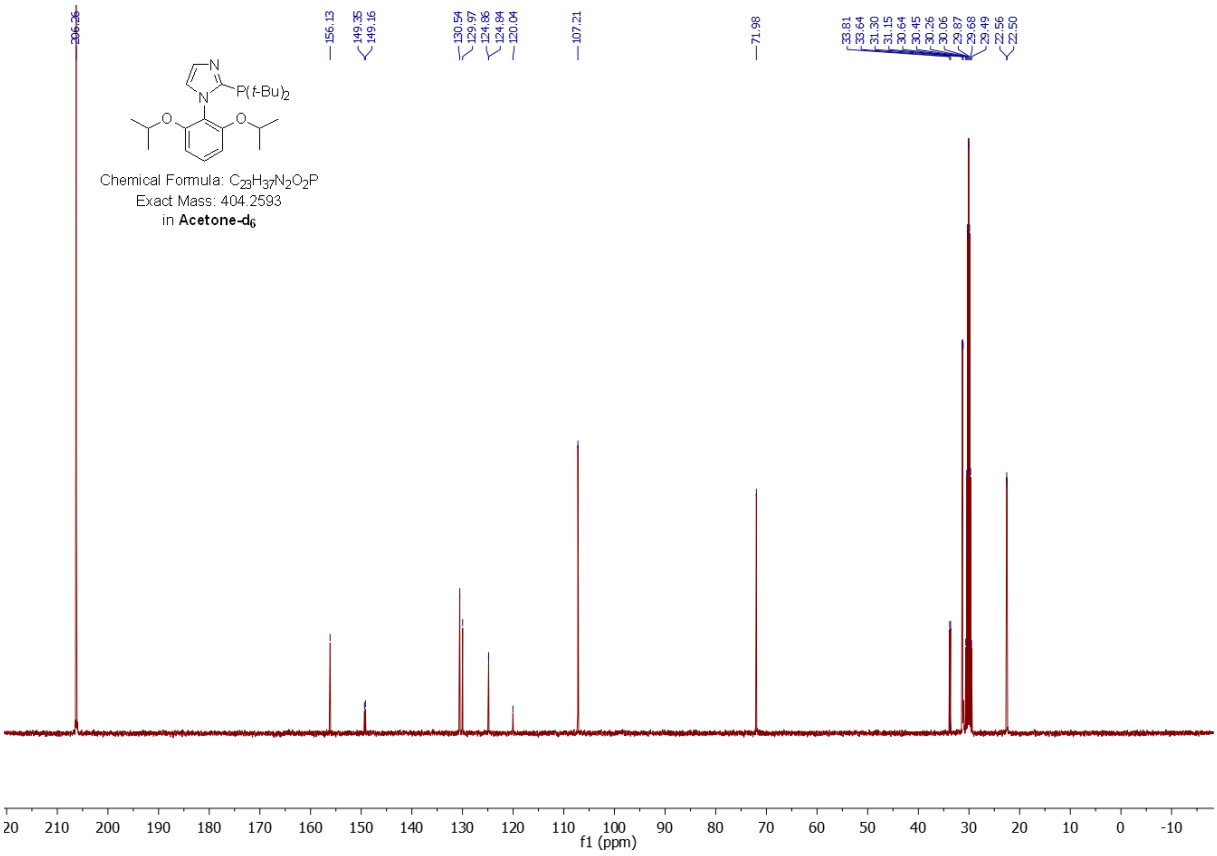

PCy2
Chemical Formula: C27H41N2O2P
Exact Mass: 456.2906
in Acetone-d6
f1 (ppm)

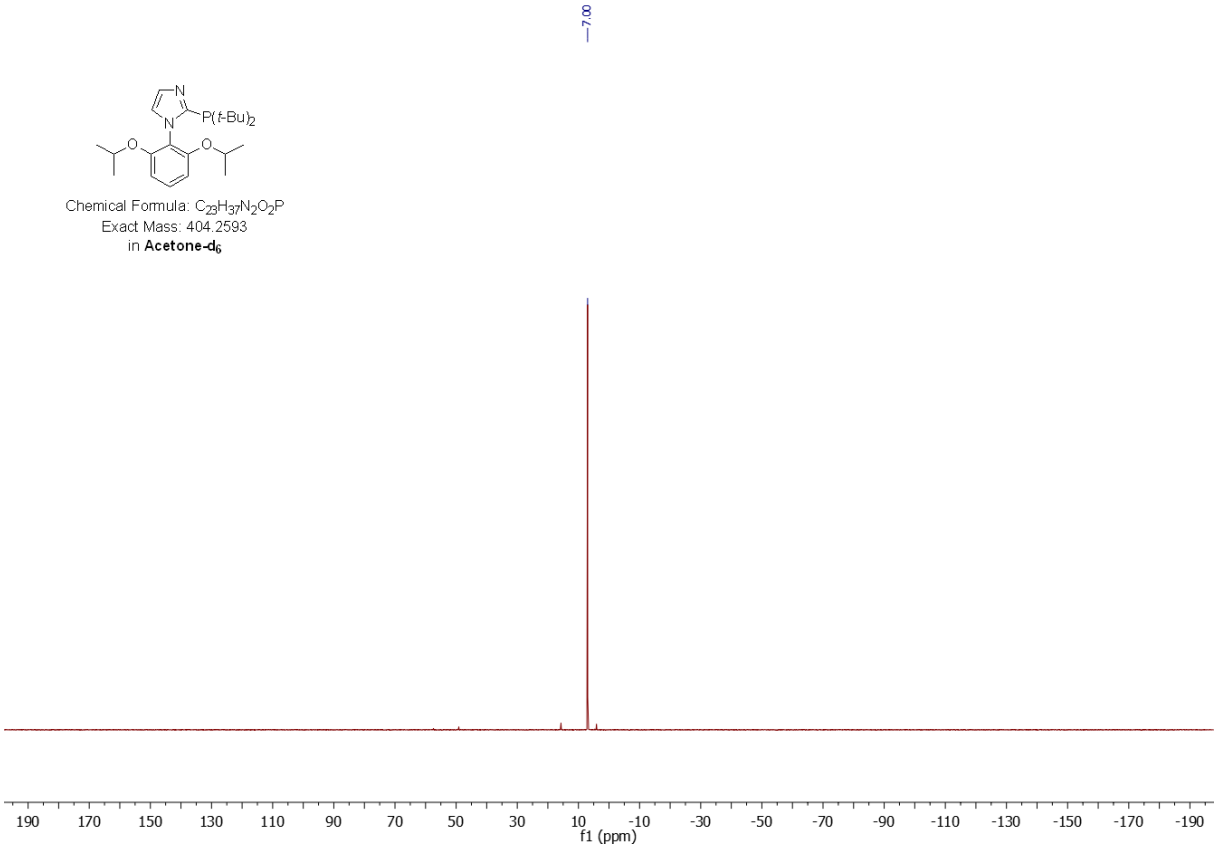


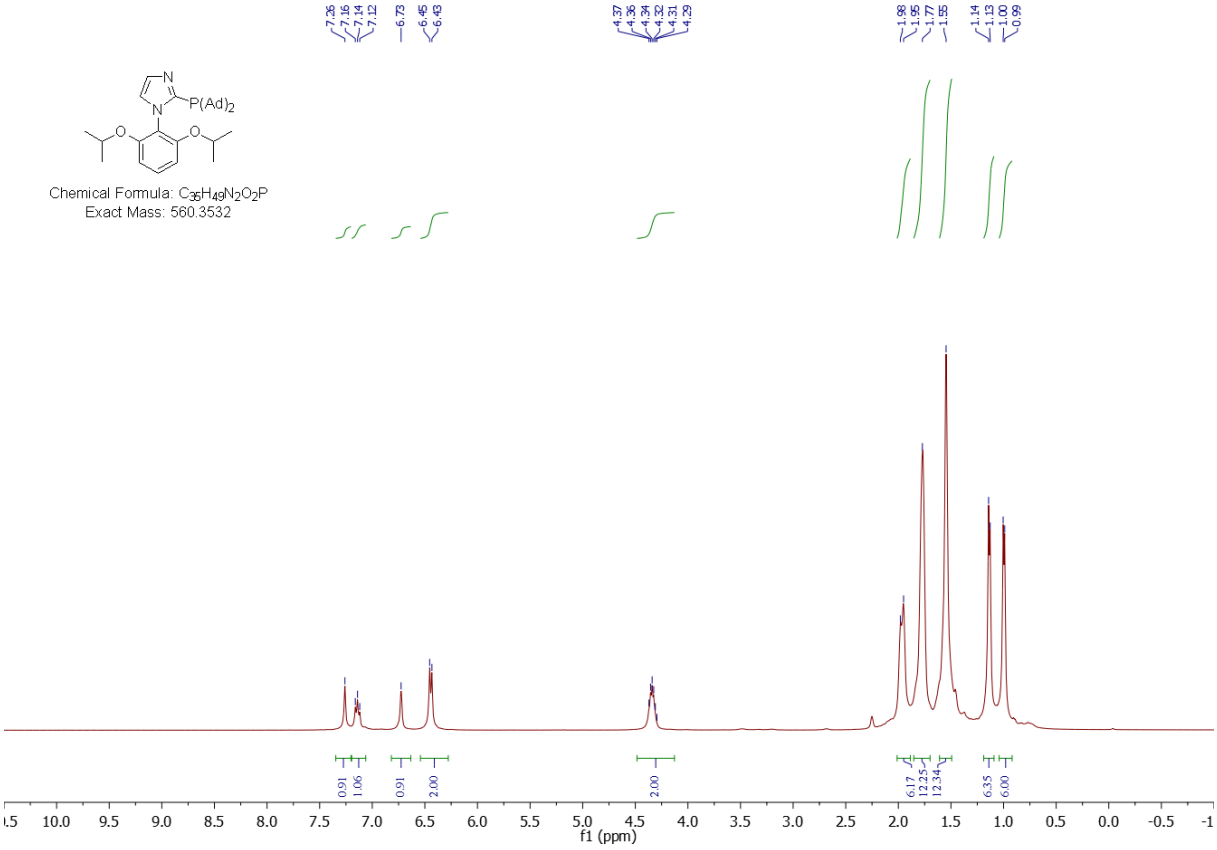
Chemical Formula: $C_{27}H_{41}N_2O_2P$
Exact Mass: 456.2906
in **Acetone-d_6**

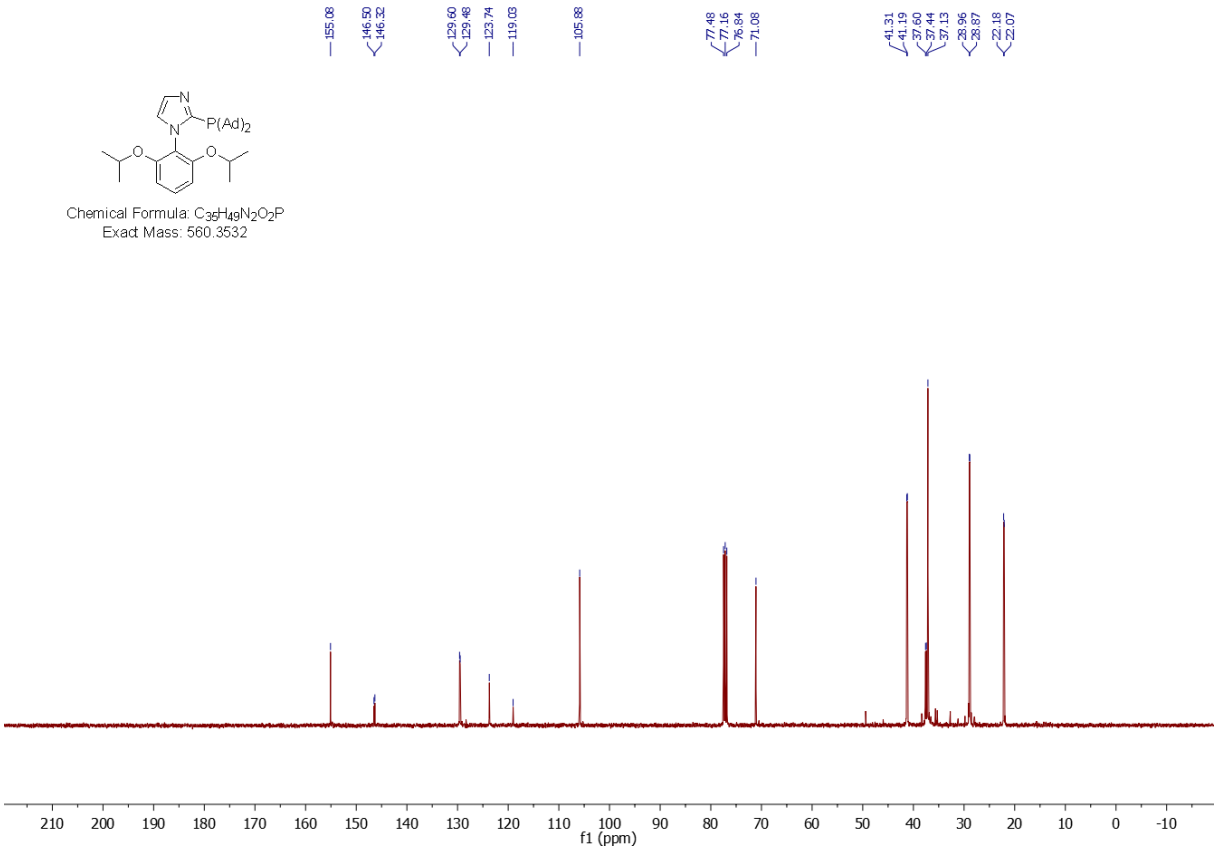


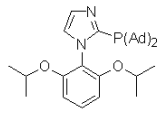
Chemical Formula: $C_{23}H_{37}N_2O_2P$
Exact Mass: 404.2593
in **Acetone-d_6**


206.26
156.13
149.35
149.16
130.54
129.97
124.86
124.84
120.04
107.21
71.98
33.81
33.64
31.30
31.15
30.64
30.45
30.26
30.06
29.87
29.68
29.49
22.56
22.50
P(t-Bu)2
Chemical Formula: C23H37N2O2P
Exact Mass: 404.2593
in Acetone-d6
f1 (ppm)

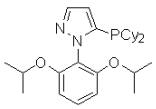

7.00
P(t-Bu)2
Chemical Formula: C23H37N2O2P
Exact Mass: 404.2593
in Acetone-d6
f1 (ppm)


P(Ad)2
Chemical Formula: C36H49N2O2P
Exact Mass: 560.3532
f1 (ppm)

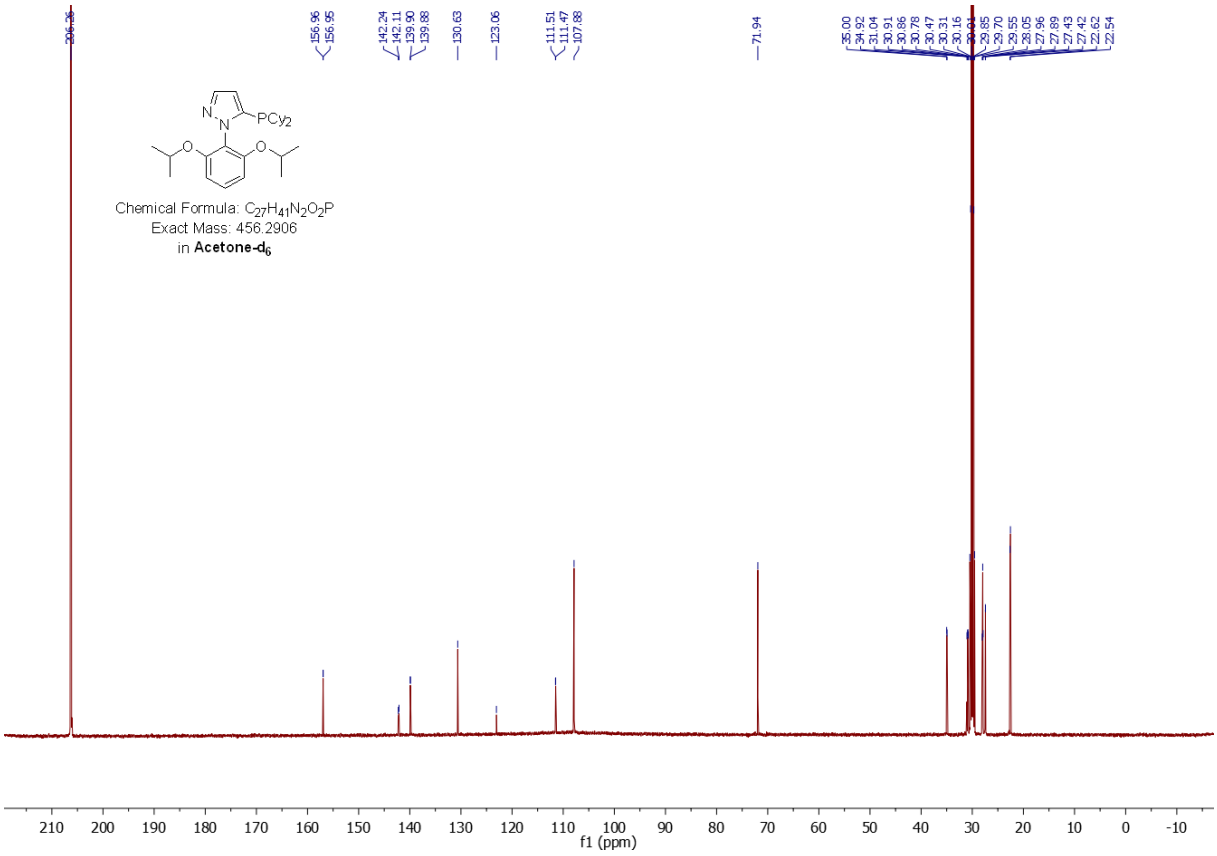

P(Ad)2
Chemical Formula: C36H49N2O2P
Exact Mass: 560.3532
f1 (ppm)

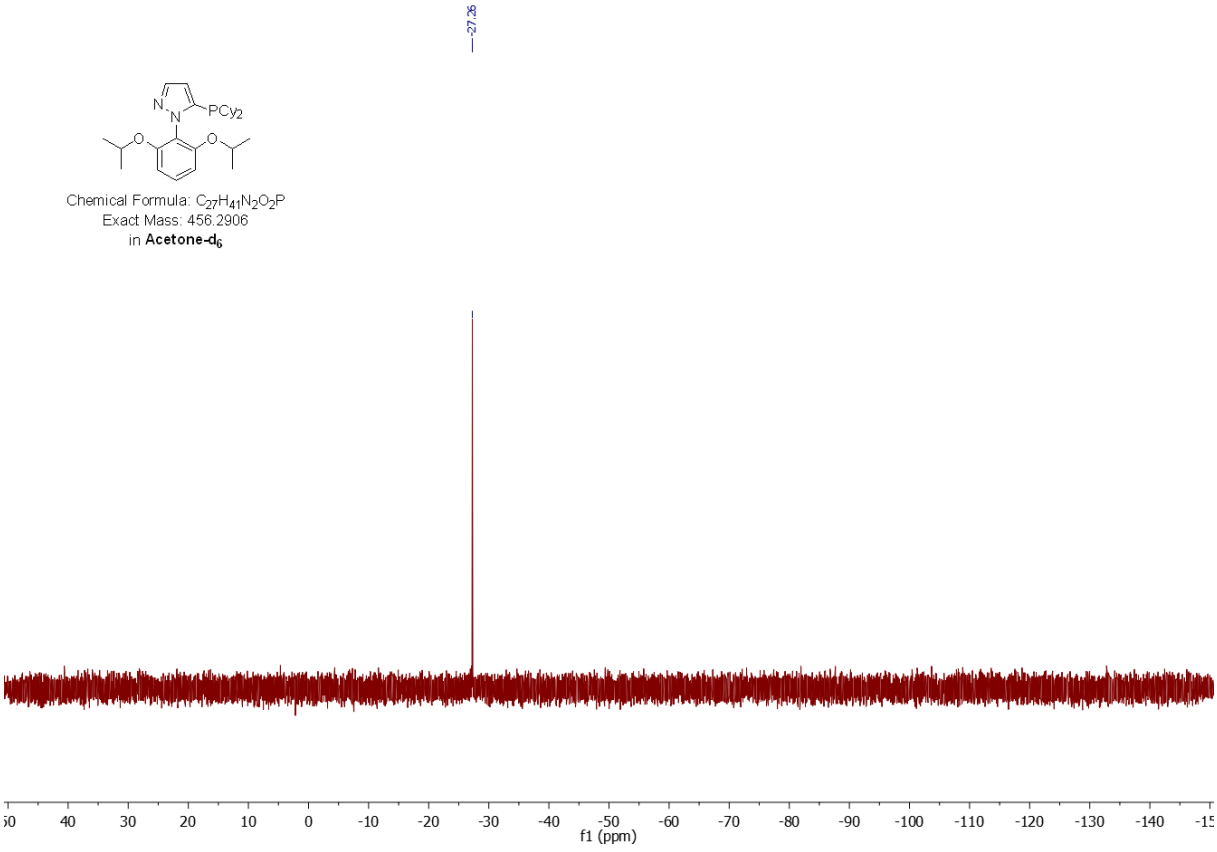


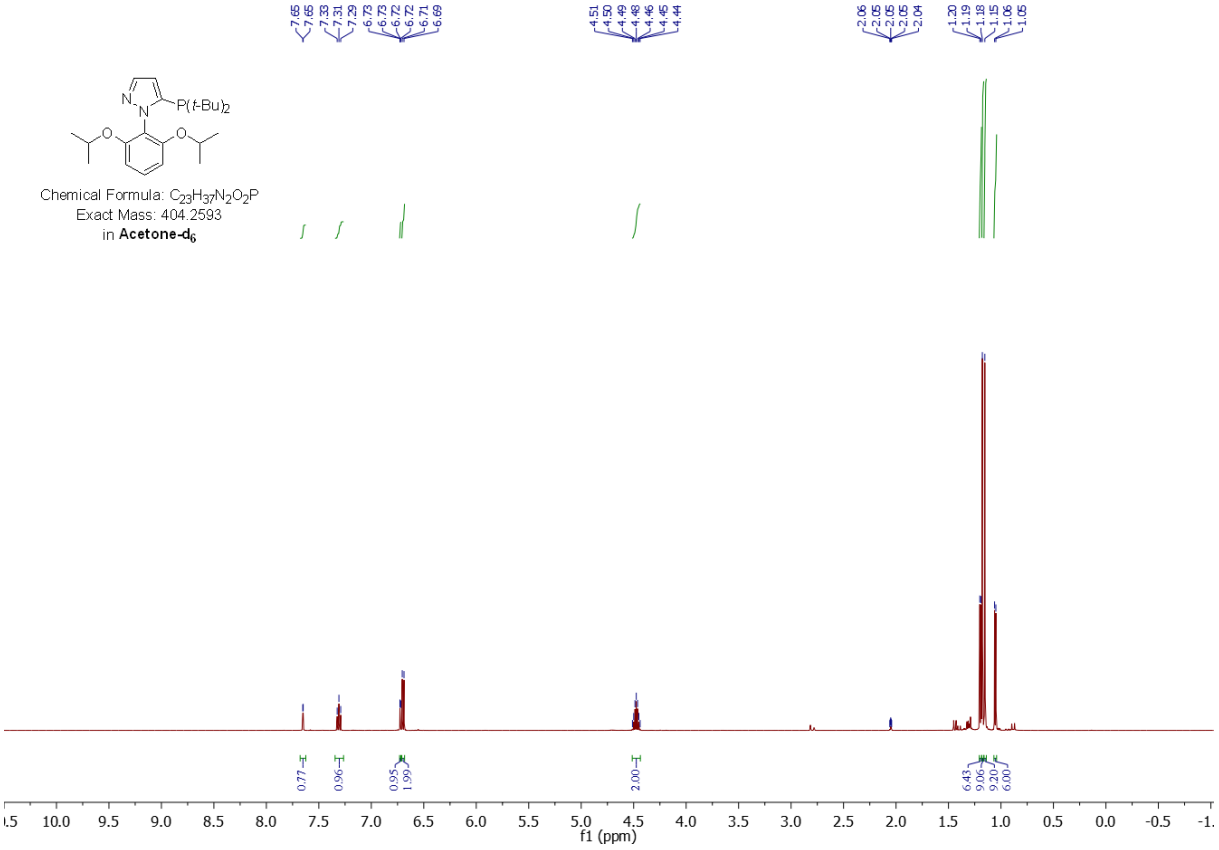
Chemical Formula: $C_{35}H_{49}N_2O_2P$
Exact Mass: 560.3532

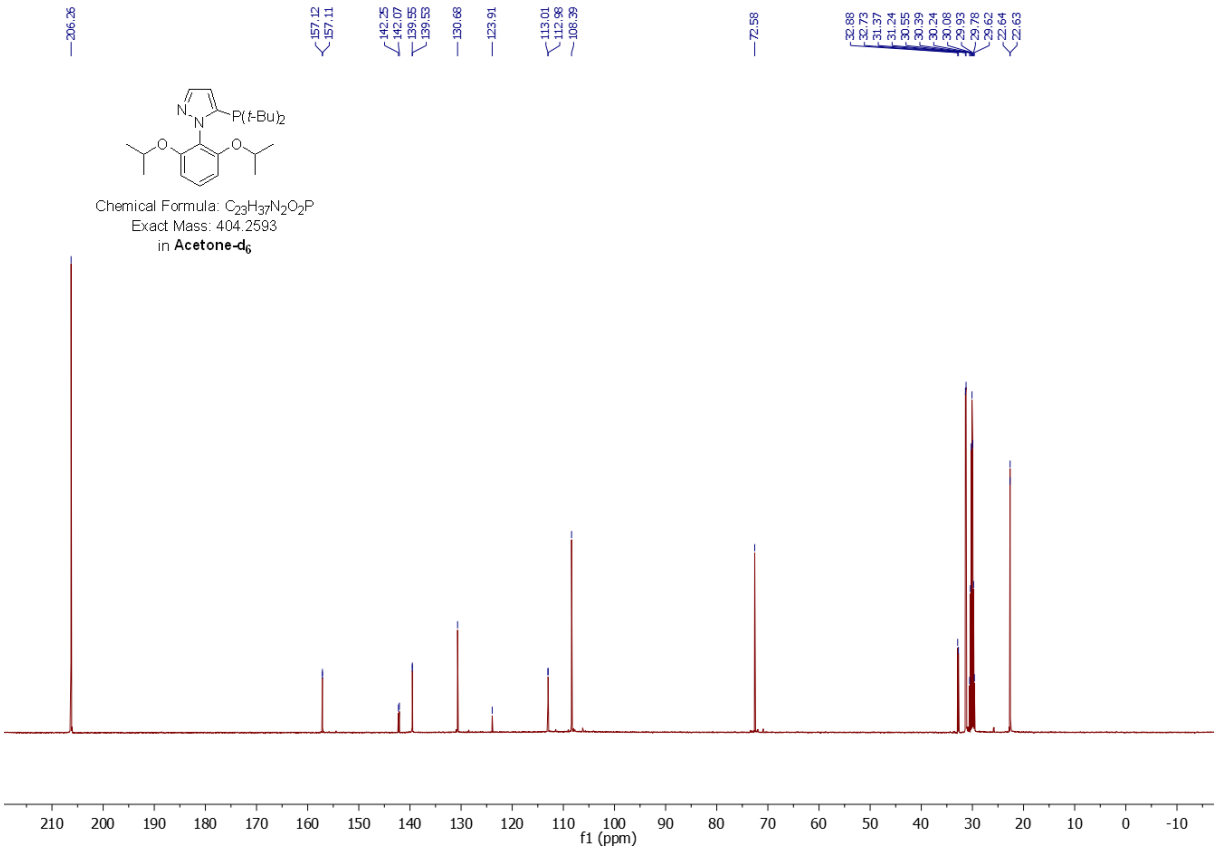


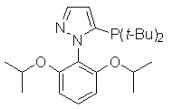
Chemical Formula: $C_{27}H_{41}N_2O_2P$
Exact Mass: 456.2906
in **Acetone-d_6**


206.26
156.96
156.95
142.24
142.11
139.90
139.88
130.63
123.06
111.51
111.47
107.88
71.94
35.00
34.92
31.04
30.91
30.86
30.78
30.47
30.31
30.16
29.85
29.70
29.55
28.05
27.96
27.89
27.43
27.42
22.62
22.54
PCy2
Chemical Formula: C27H41N2O2P
Exact Mass: 456.2906
in Acetone-d6
f1 (ppm)


27.26
PCy2
Chemical Formula: C27H41N2O2P
Exact Mass: 456.2906
in Acetone-d6
f1 (ppm)

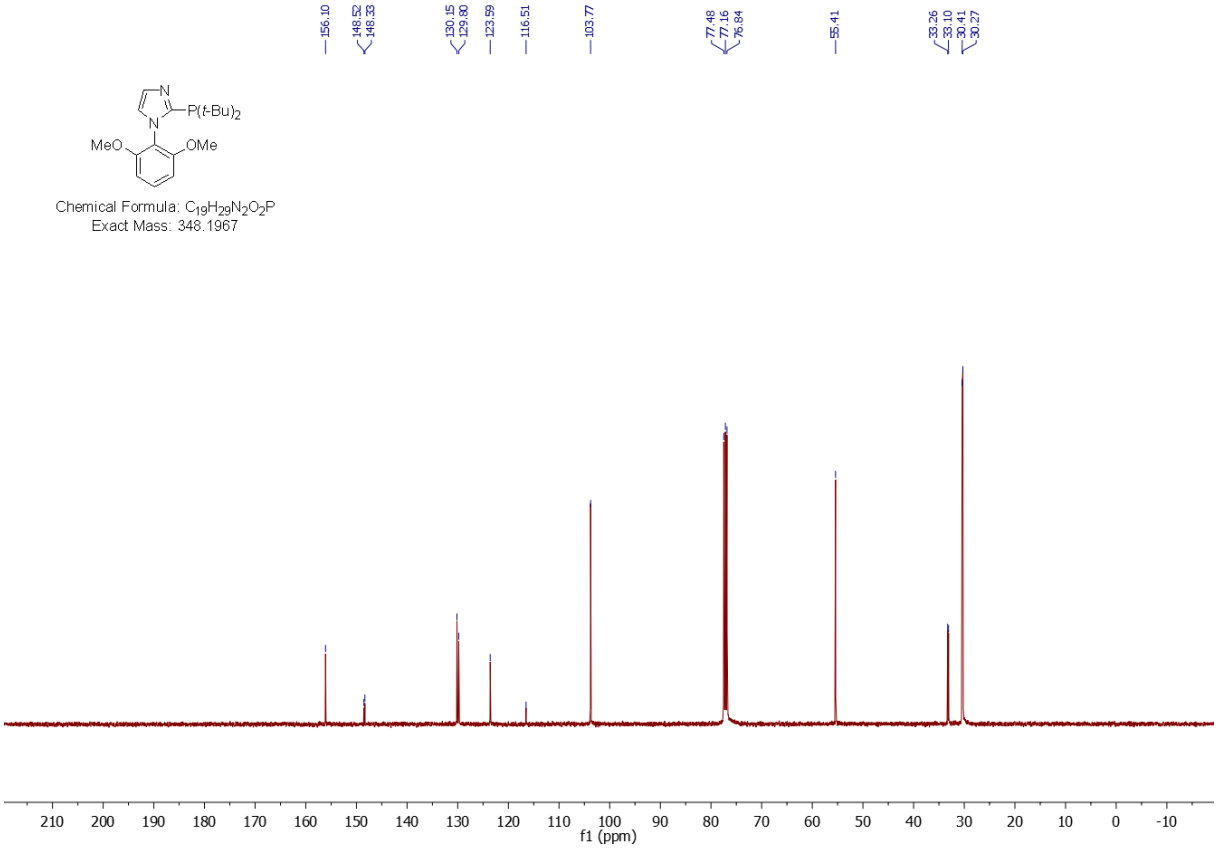

7.65
7.65
7.33
7.31
7.29
6.73
6.73
6.72
6.72
6.71
6.69
4.51
4.50
4.49
4.48
4.46
4.45
4.44
2.06
2.05
2.05
2.05
2.04
1.20
1.19
1.18
1.15
1.06
1.05
P(t-Bu)2
Chemical Formula: C23H37N2O2P
Exact Mass: 404.2593
in Acetone-d6
0.77
0.96
0.95
1.99
2.00
6.43
9.06
9.20
6.00
f1 (ppm)

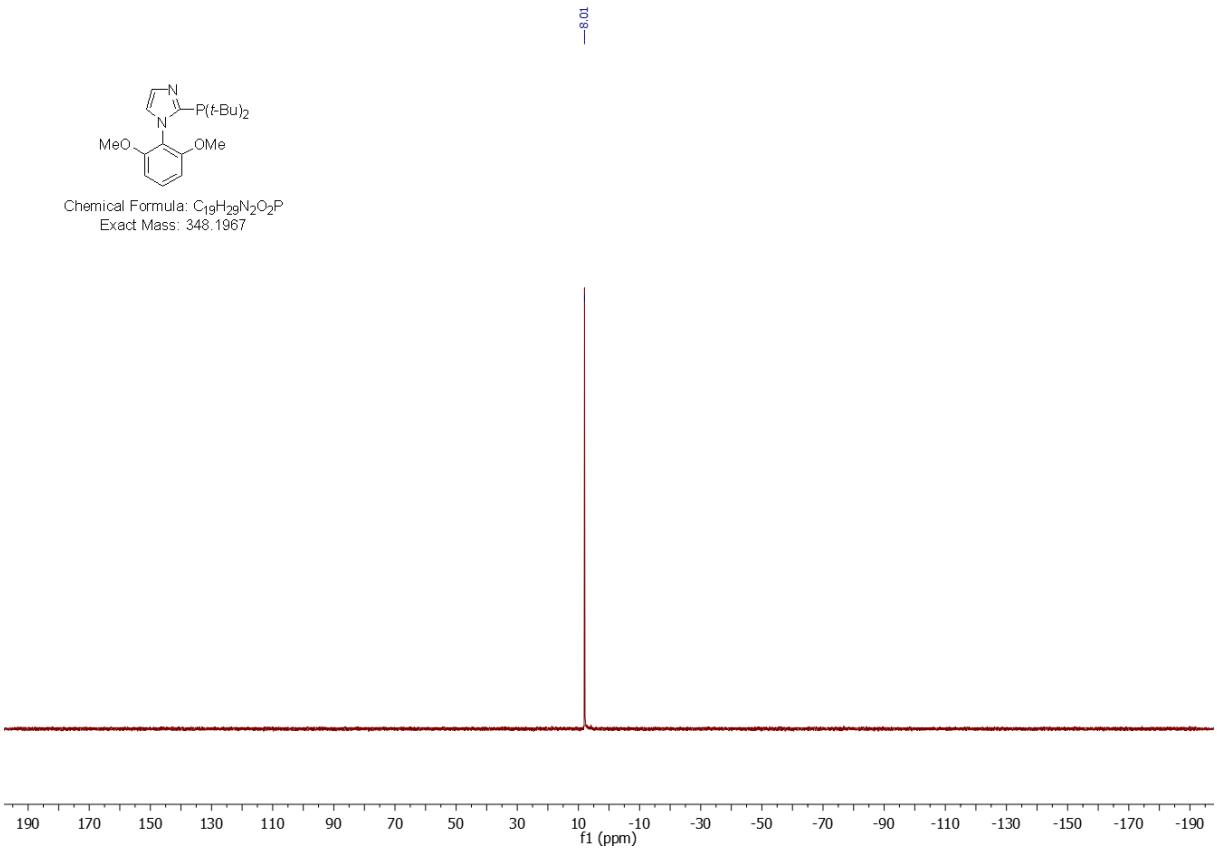

206.26
157.12
157.11
142.25
142.07
139.55
139.53
130.68
123.91
113.01
112.98
108.39
72.58
32.88
32.73
31.37
31.24
30.55
30.39
30.24
30.08
29.93
29.78
29.62
22.64
22.63
P(t-Bu)2
Chemical Formula: C23H37N2O2P
Exact Mass: 404.2593
in Acetone-d6
f1 (ppm)

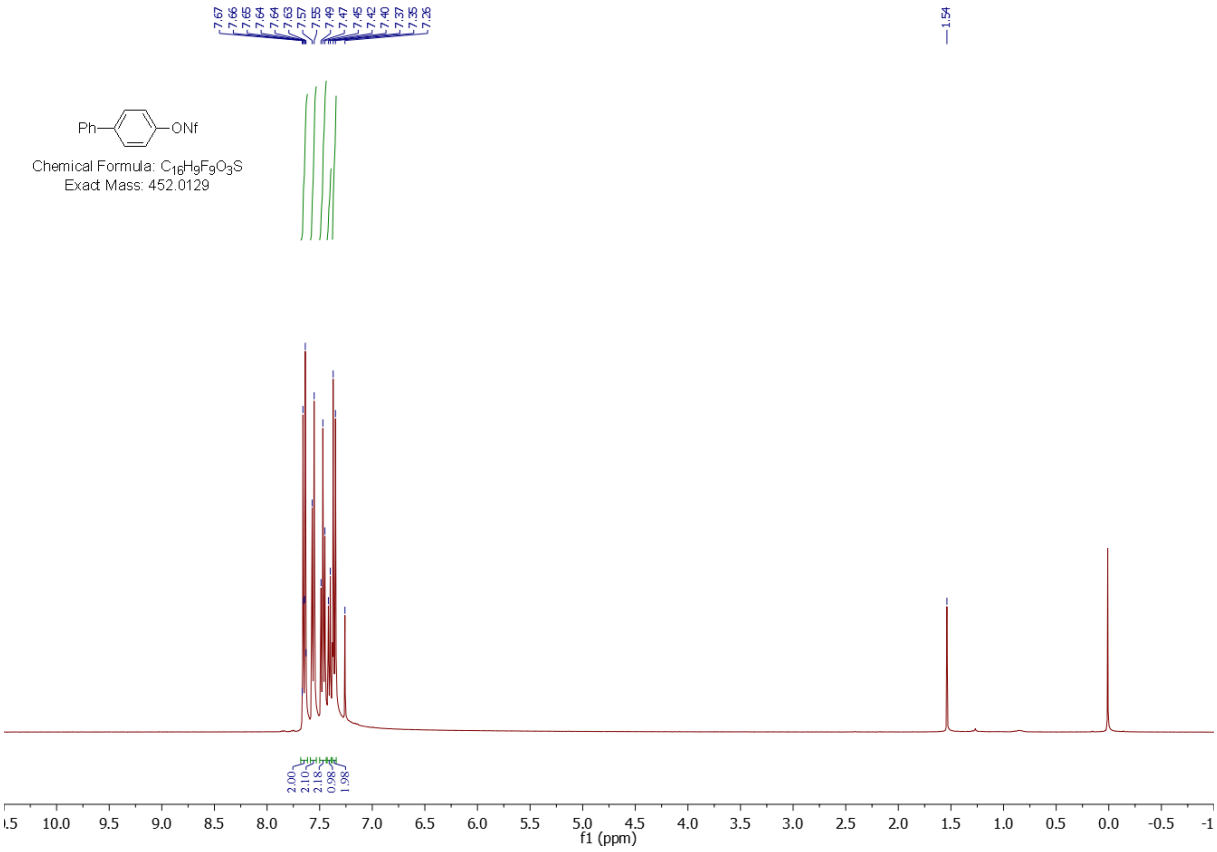


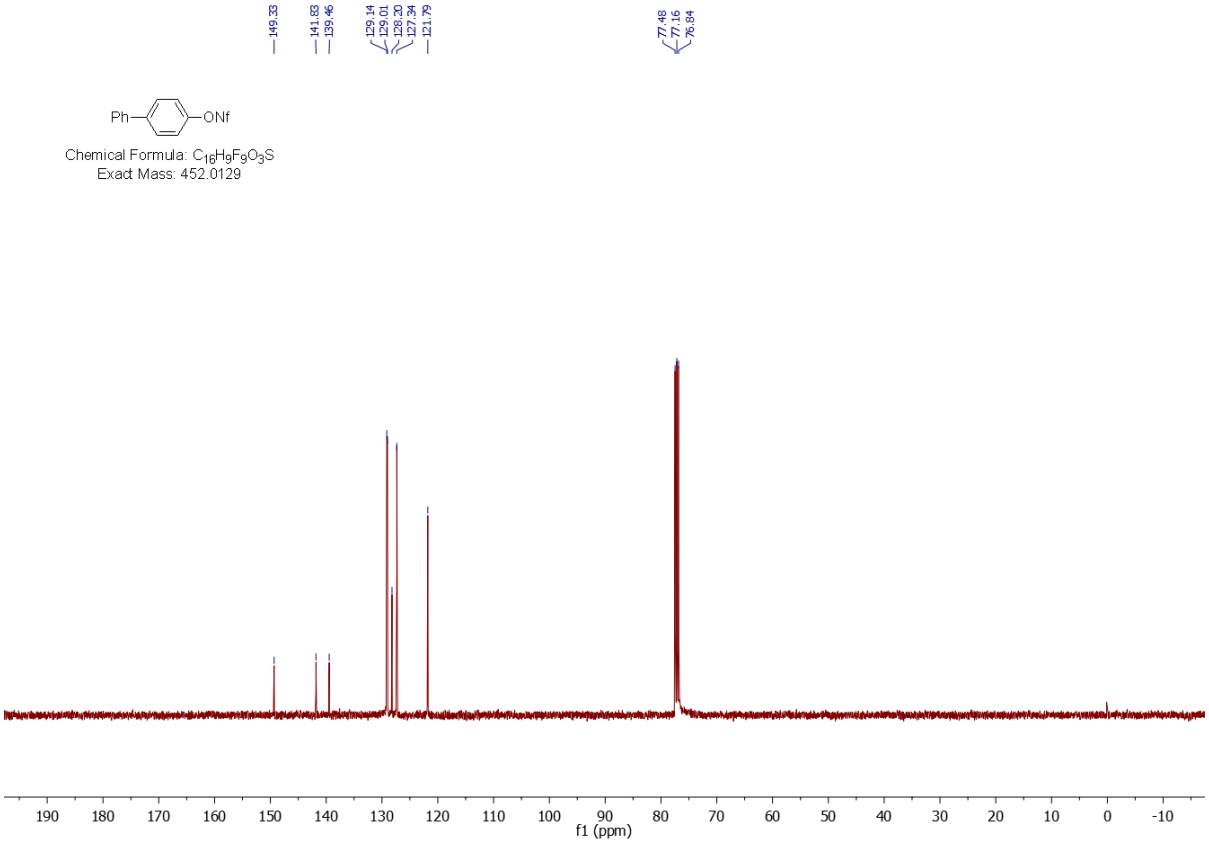
Chemical Formula: $C_{23}H_{37}N_2O_2P$
Exact Mass: 404.2593
in **Acetone-d_6**

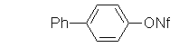
Chemical Formula: $C_{19}H_{29}N_2O_2P$
Exact Mass: 348.1967


156.10
148.52
148.33
130.15
129.80
123.59
116.51
103.77
77.48
77.16
76.84
55.41
33.26
33.10
30.41
30.27
N
P(t-Bu)2
N
MeO
OMe
Chemical Formula: C19H29N2O2P
Exact Mass: 348.1967
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

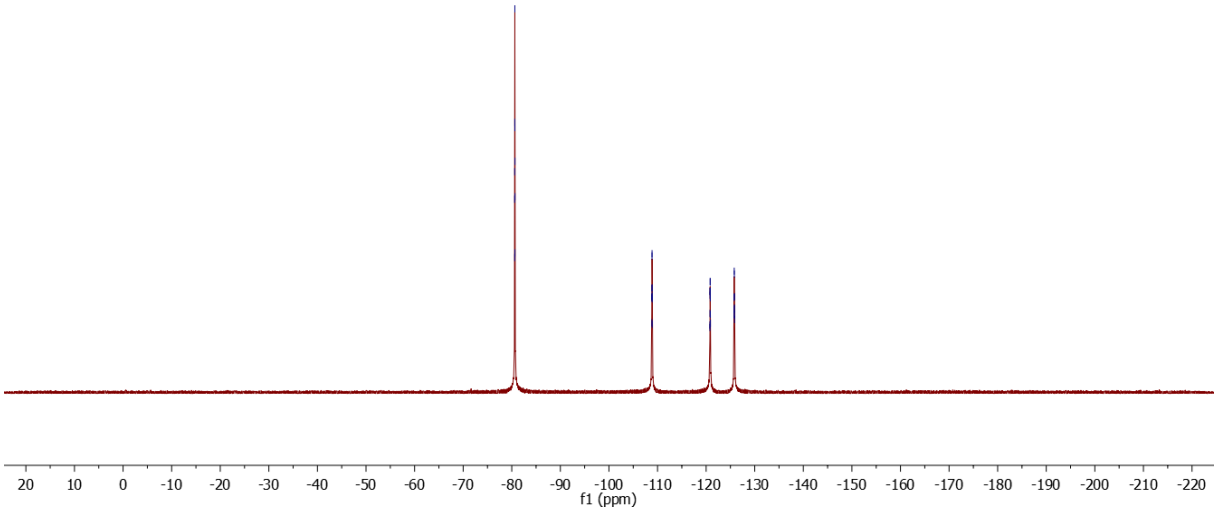

8.01
N
P(t-Bu)2
N
MeO
OMe
Chemical Formula: C19H29N2O2P
Exact Mass: 348.1967
190 170 150 130 110 90 70 50 30 10 -10 -30 -50 -70 -90 -110 -130 -150 -170 -190
f1 (ppm)

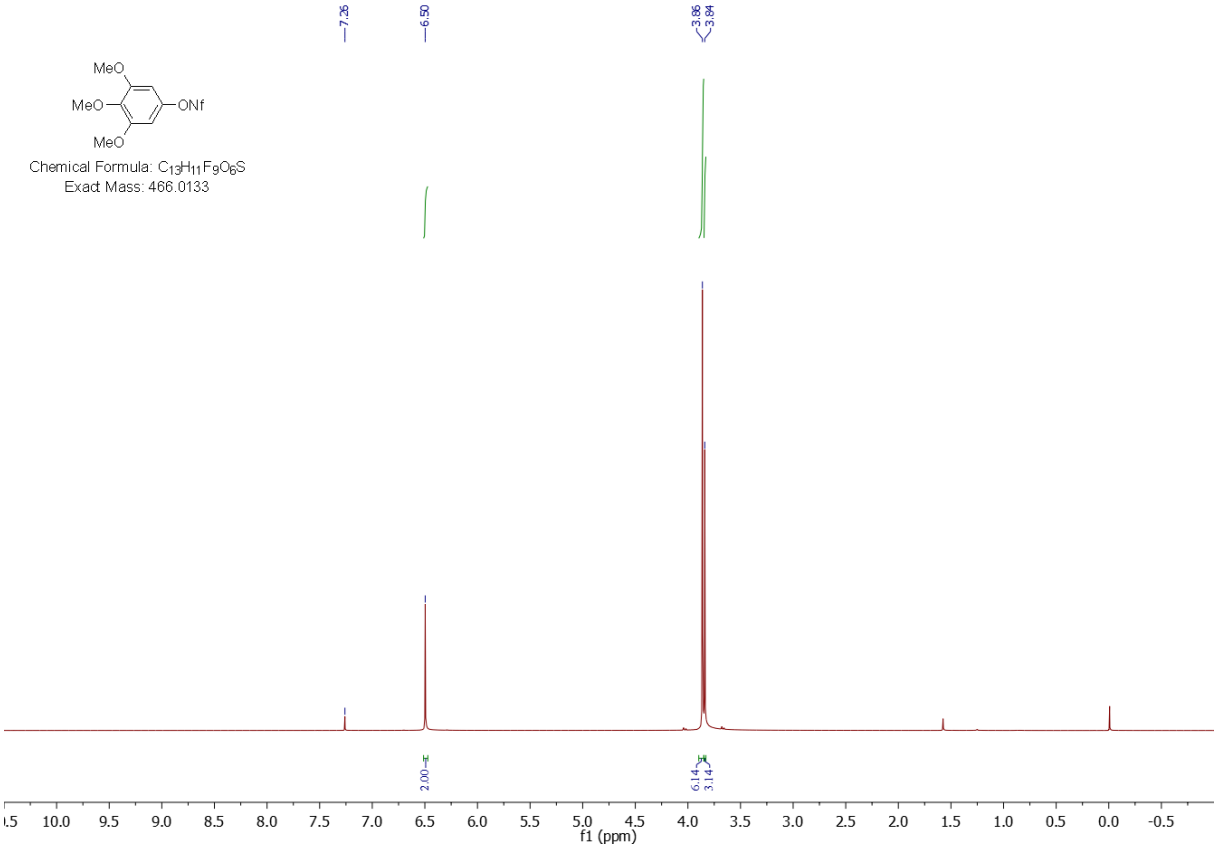

7.67
7.66
7.65
7.64
7.64
7.63
7.57
7.55
7.49
7.47
7.45
7.42
7.40
7.37
7.35
7.26
1.54
Ph
ONf
Chemical Formula: C16H9F9O3S
Exact Mass: 452.0129
2.00
2.10
2.18
0.98
1.98
f1 (ppm)


149.33
141.83
139.46
129.14
129.01
128.20
127.34
121.79
77.48
77.16
76.84
Ph
ONf
Chemical Formula: C16H9F9O3S
Exact Mass: 452.0129
f1 (ppm)

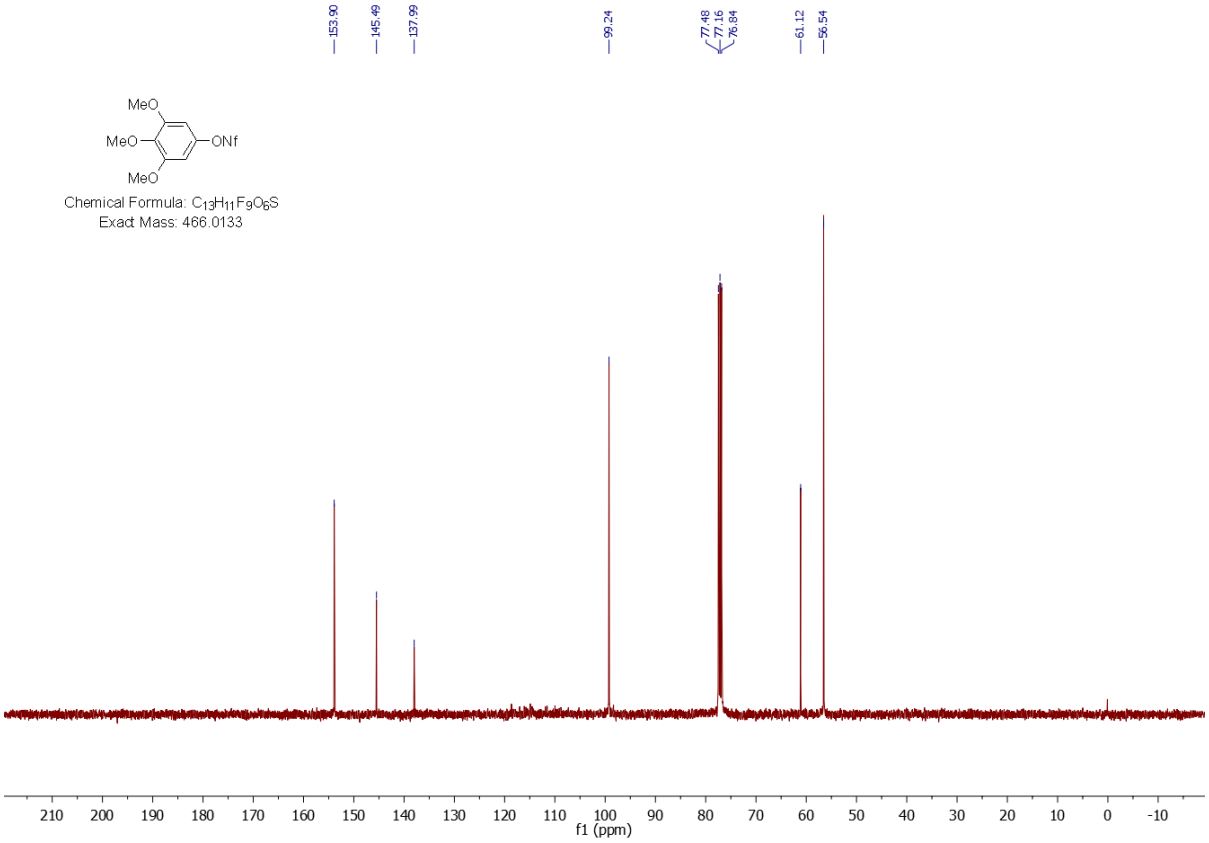


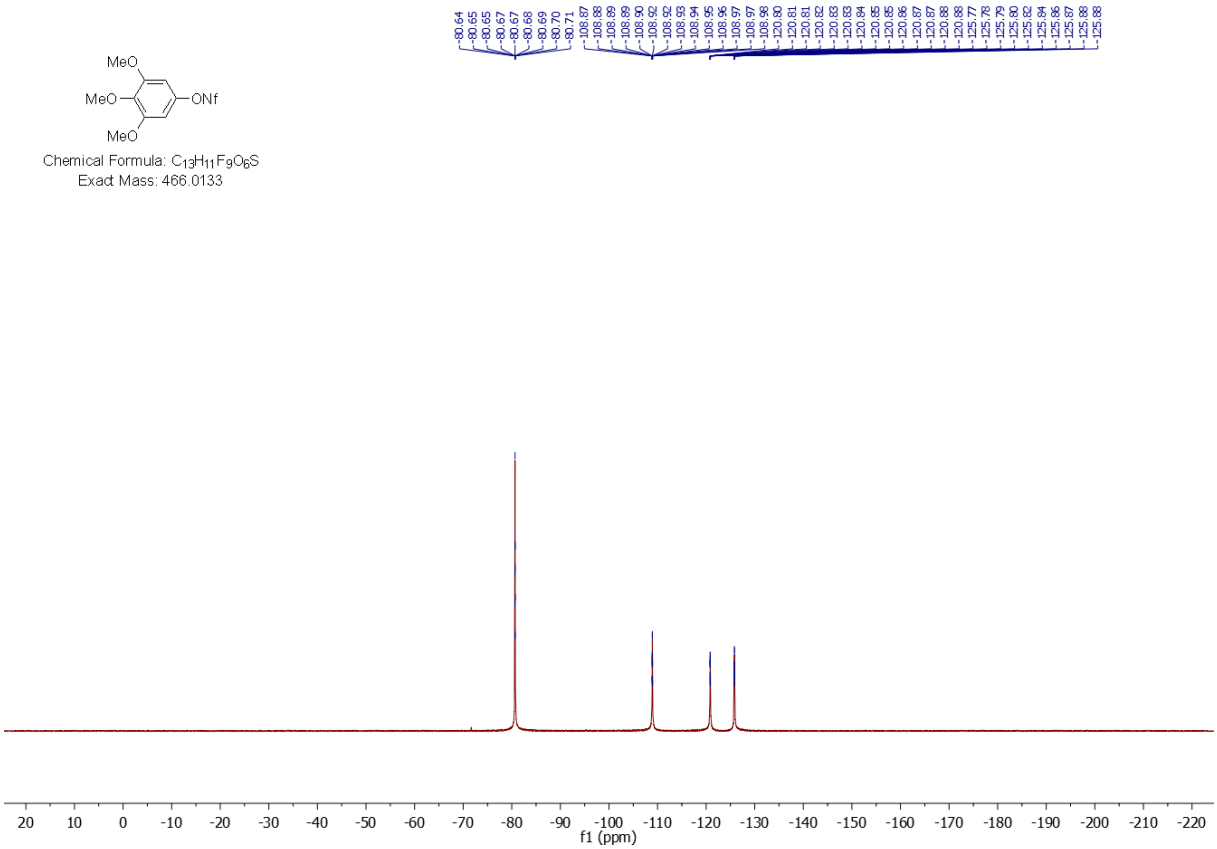
Chemical Formula: $C_{16}H_9F_9O_3S$
Exact Mass: 452.0129

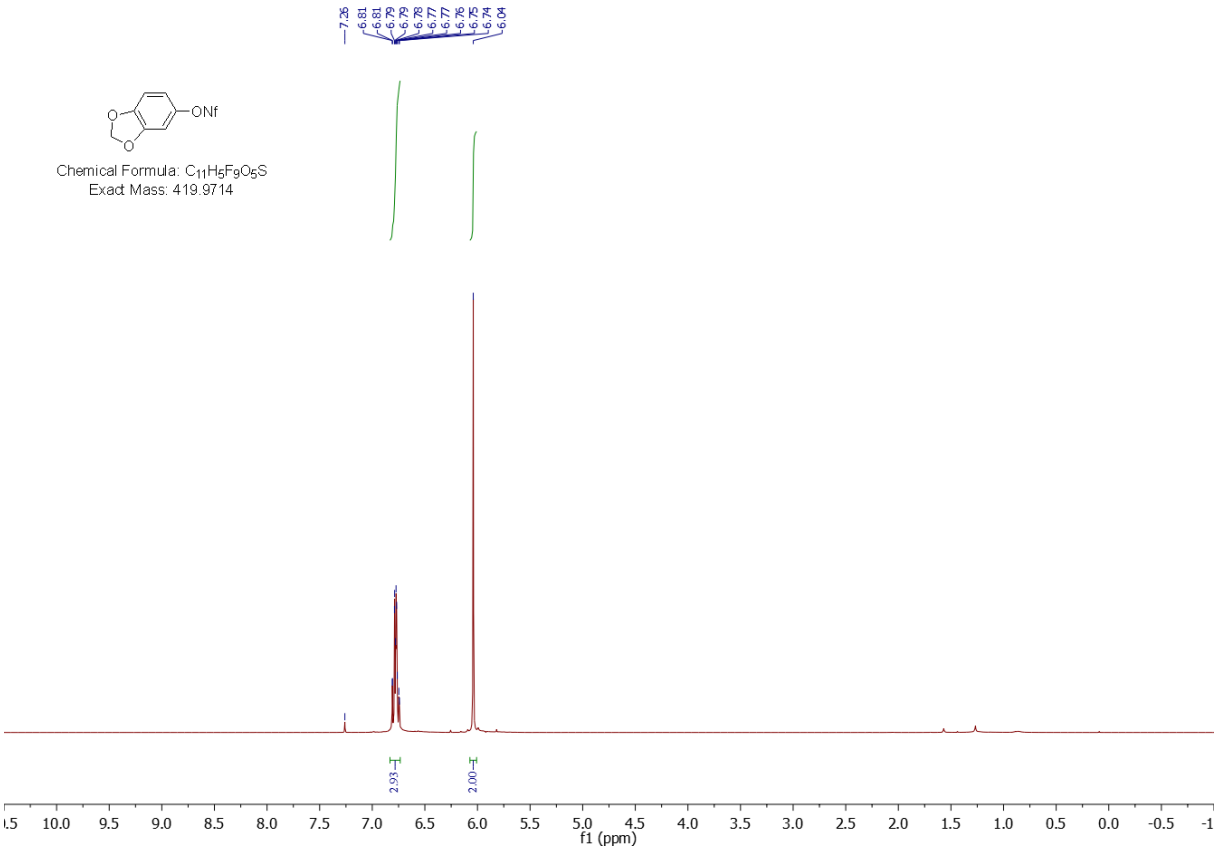


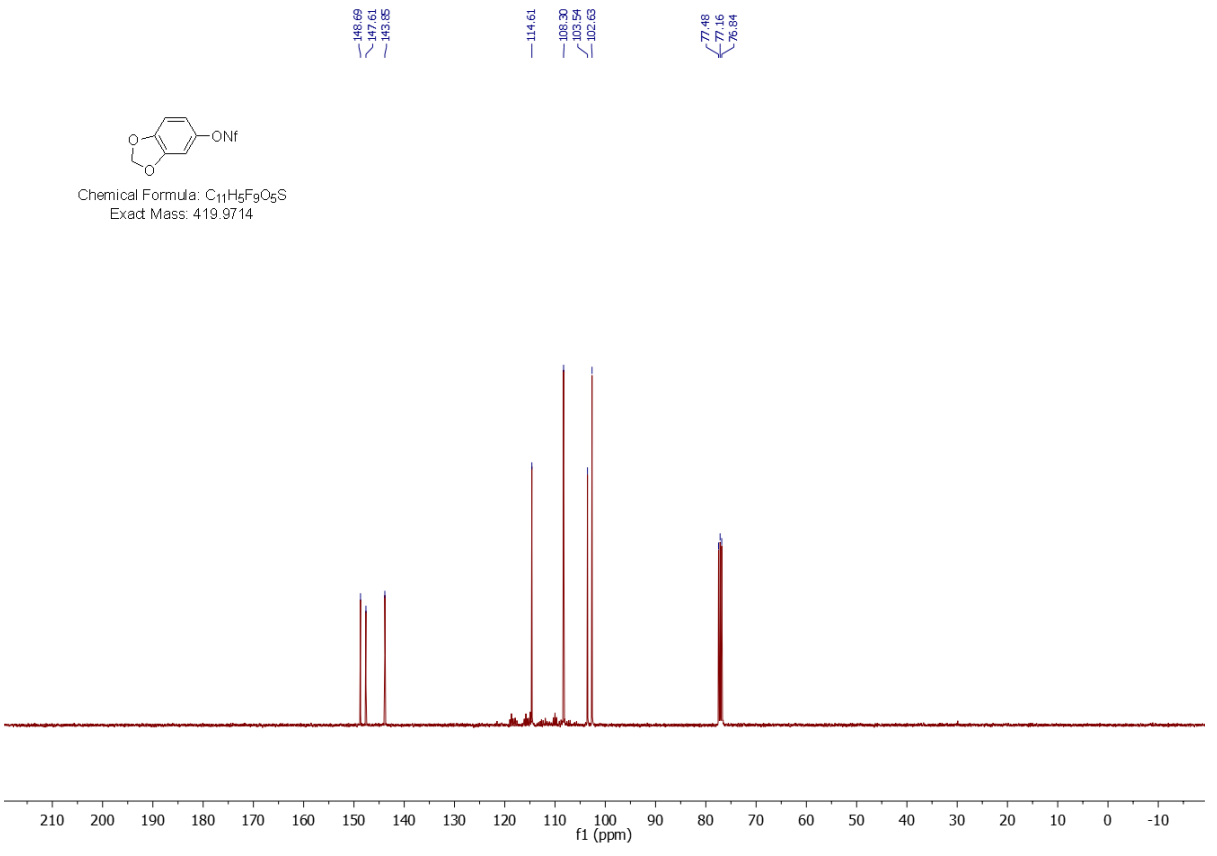


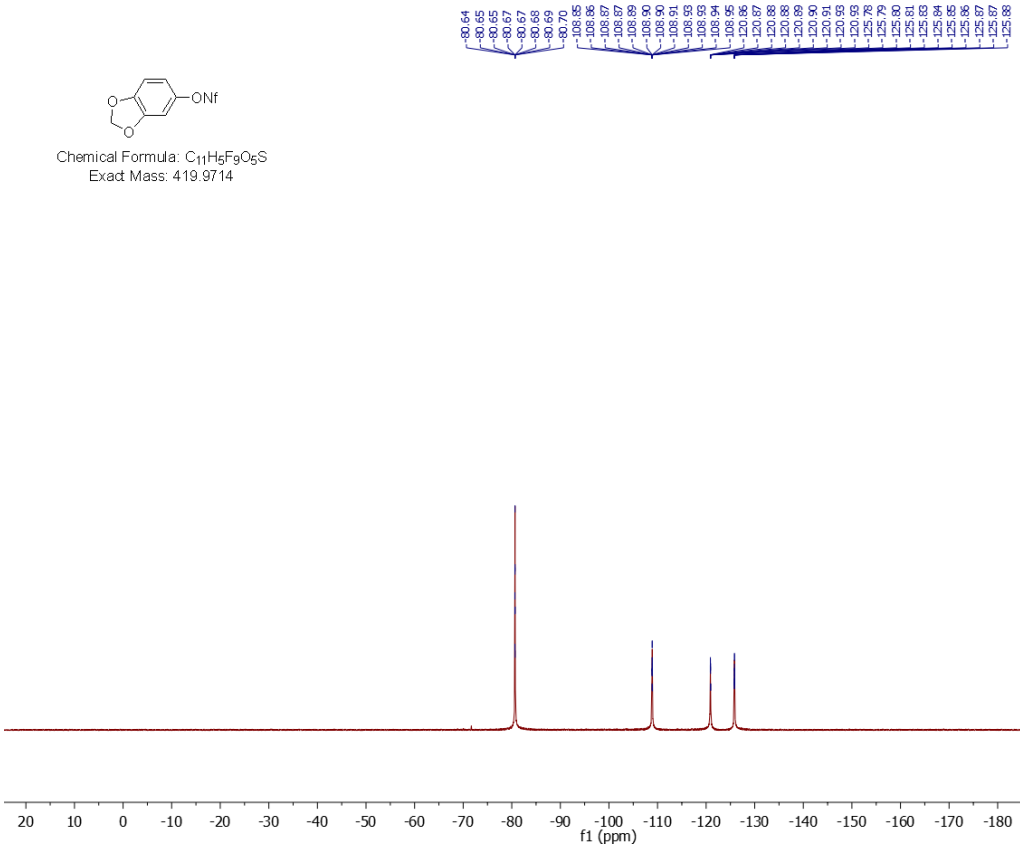
Chemical Formula: $C_{13}H_{11}F_9O_6S$
Exact Mass: 466.0133

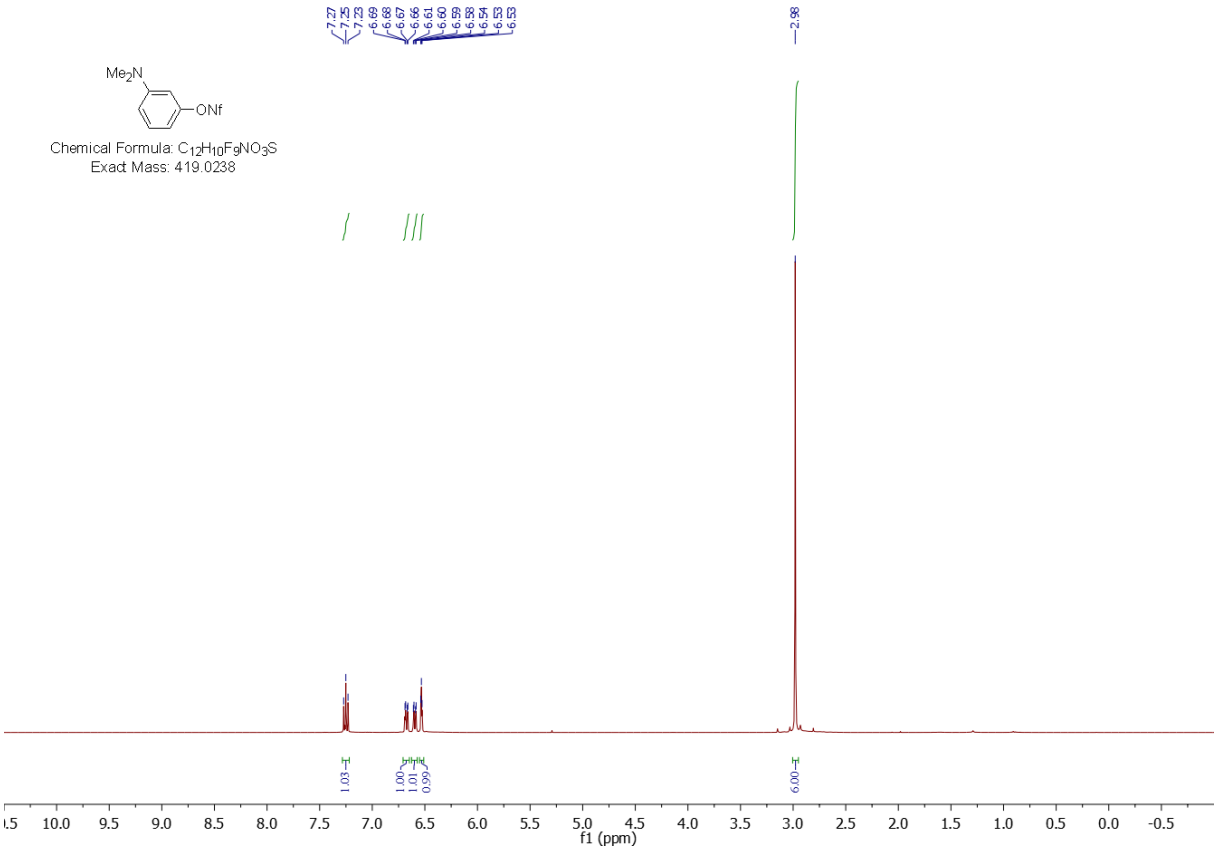

153.90
145.49
137.99
99.24
77.48
77.16
76.84
61.12
56.54
MeO
MeO
MeO
ONf
Chemical Formula: C13H11F9O6S
Exact Mass: 466.0133
f1 (ppm)

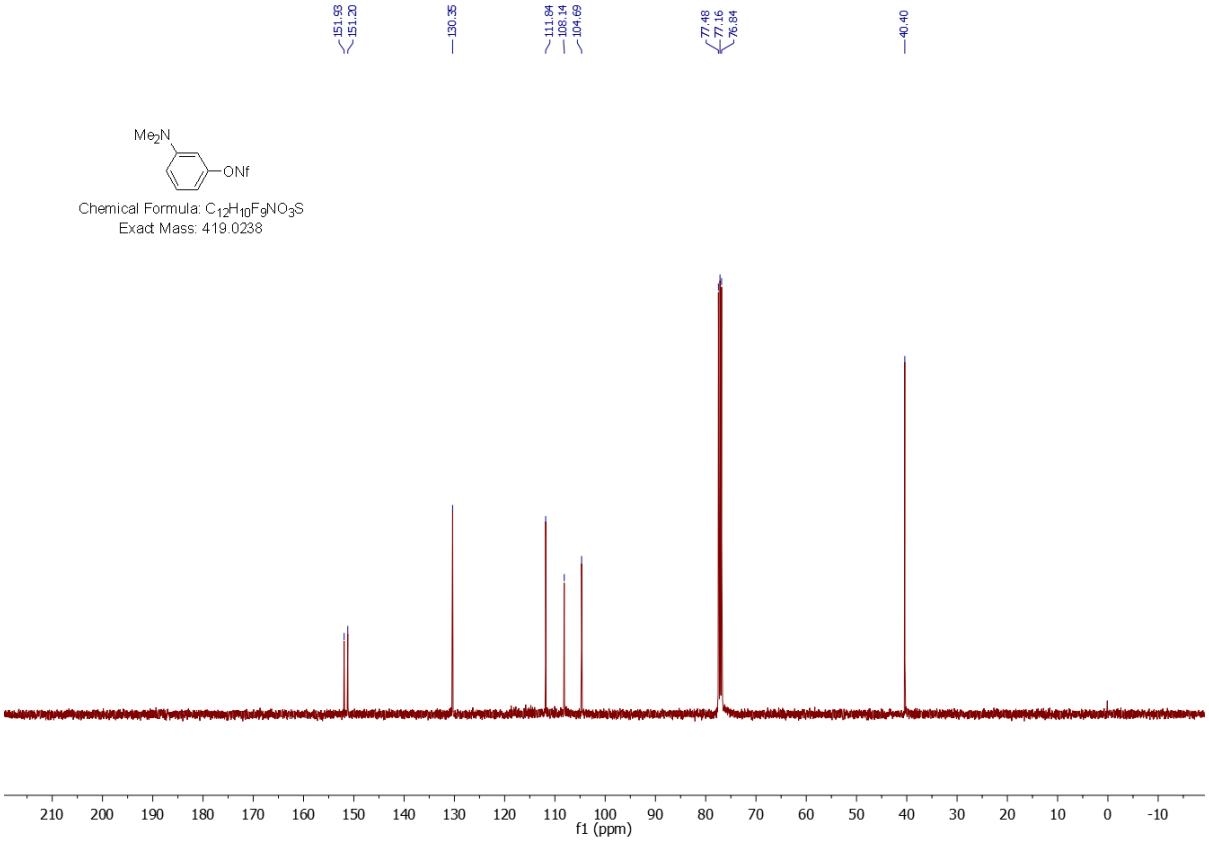

MeO
MeO
MeO
ONf
Chemical Formula: C13H11F9O6S
Exact Mass: 466.0133
f1 (ppm)

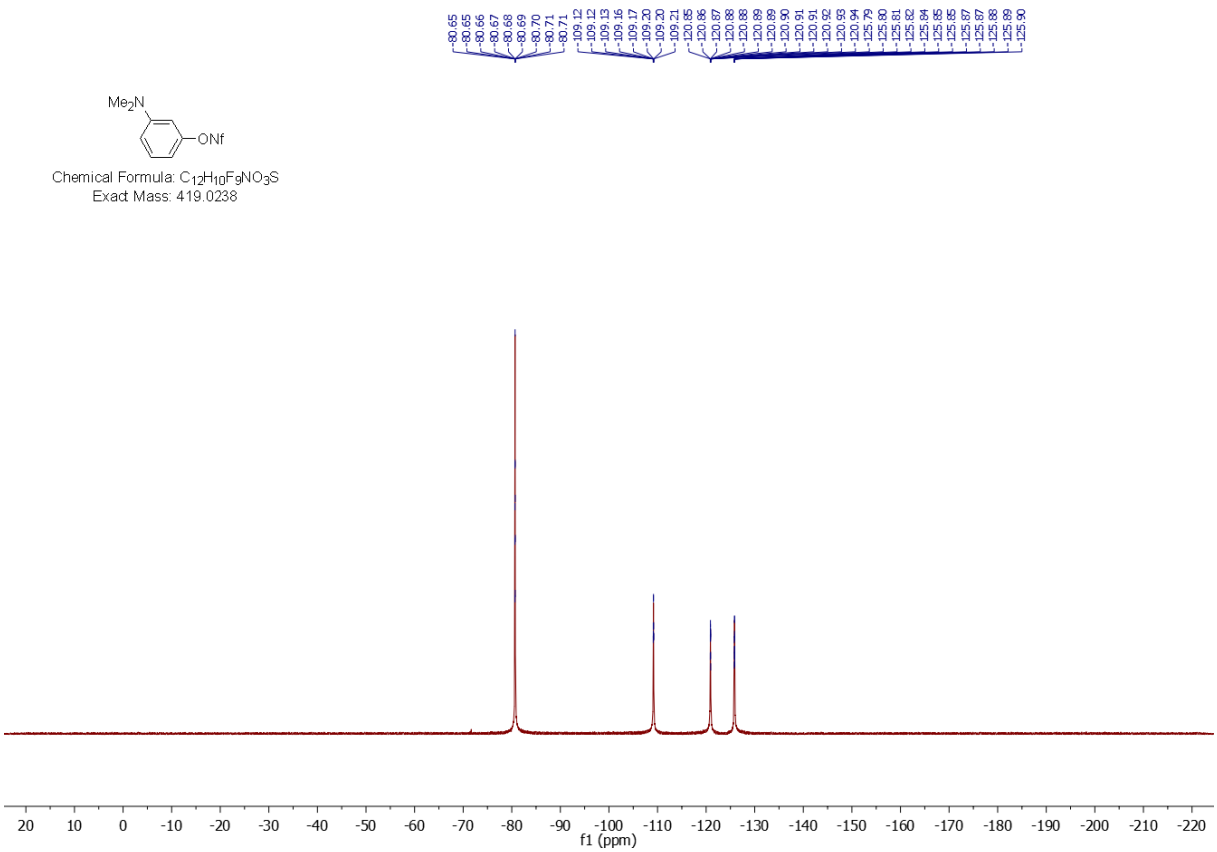

7.26
6.81
6.81
6.79
6.79
6.78
6.77
6.77
6.76
6.75
6.74
6.04
ONf
Chemical Formula: C11H5F9O5S
Exact Mass: 419.9714
2.93
2.00
f1 (ppm)

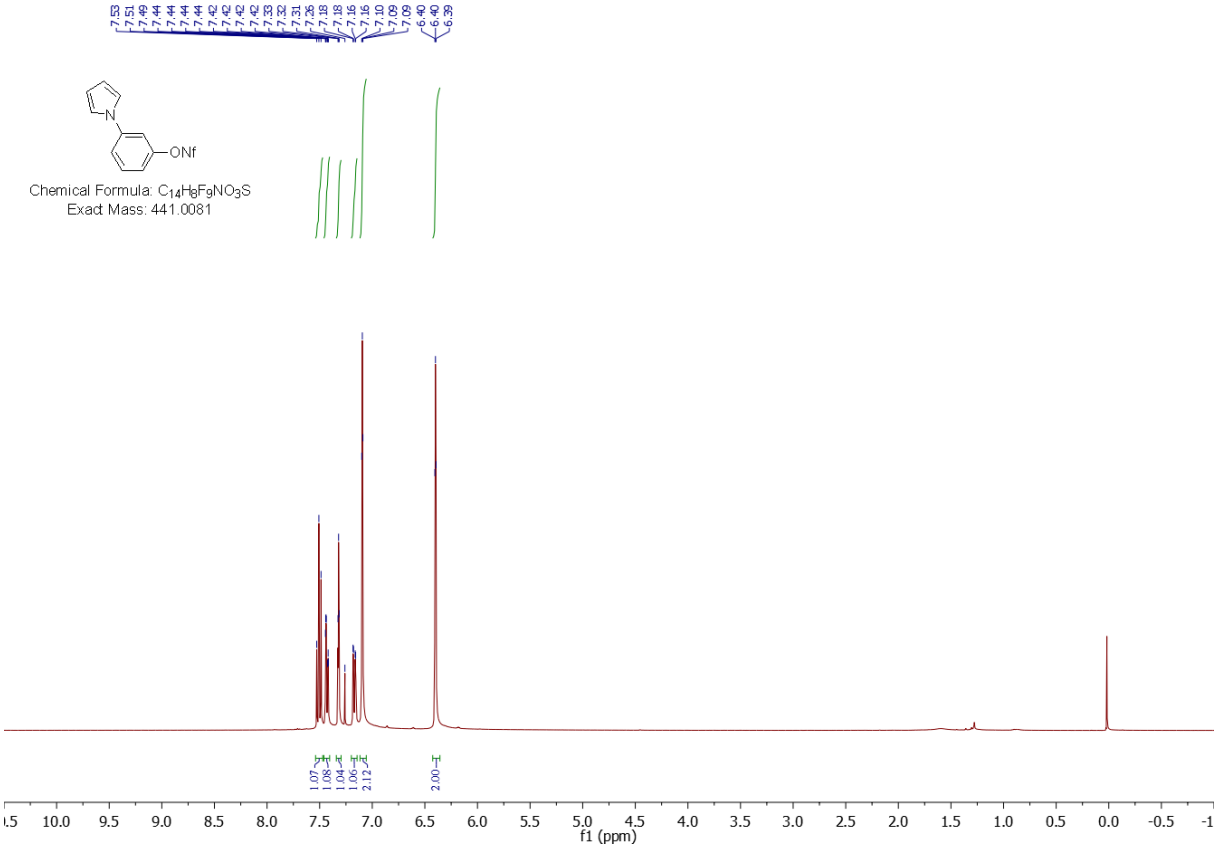

148.69
147.61
143.85
114.61
108.30
103.54
102.63
77.48
77.16
76.84
ONf
Chemical Formula: C11H5F9O5S
Exact Mass: 419.9714
f1 (ppm)

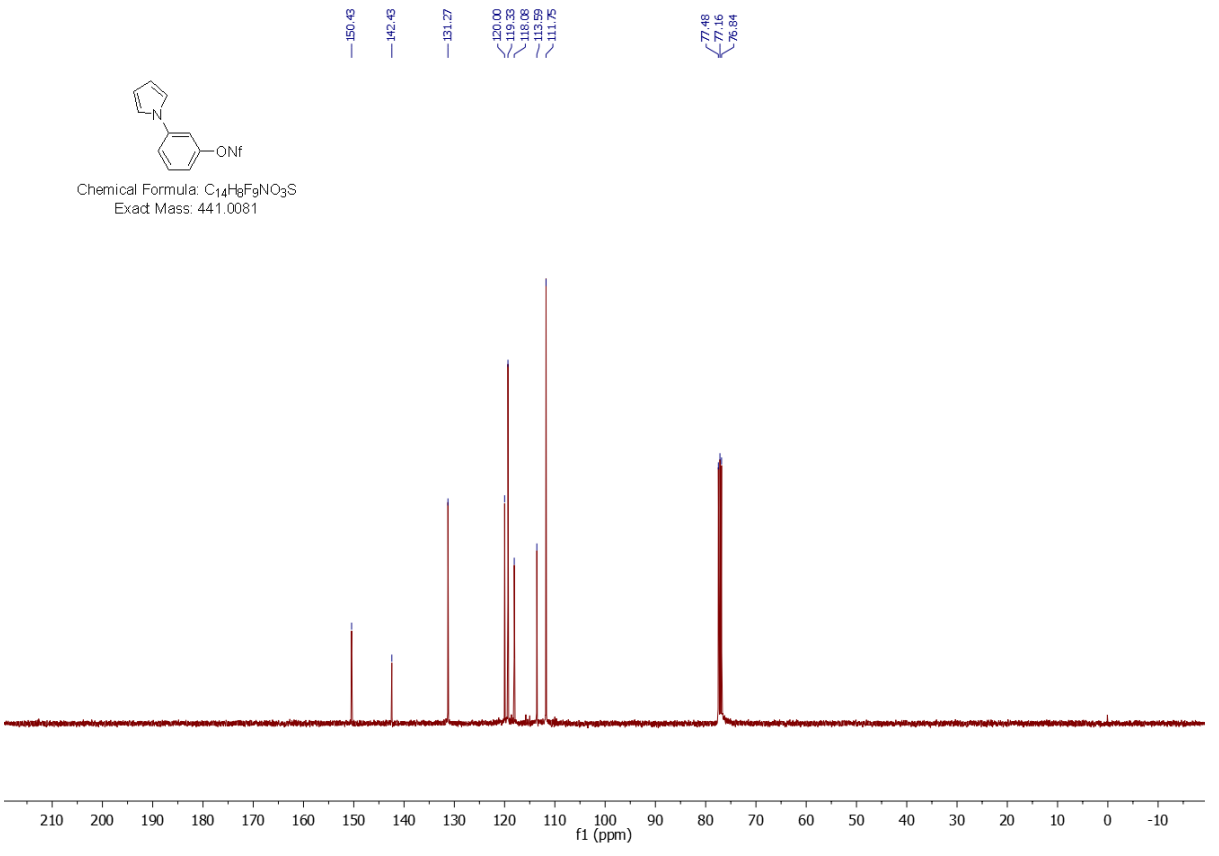

-80.64
-80.65
-80.65
-80.67
-80.67
-80.68
-80.69
-80.70
-108.85
-108.86
-108.87
-108.87
-108.89
-108.90
-108.90
-108.91
-108.93
-108.93
-108.94
-108.95
-120.86
-120.87
-120.88
-120.89
-120.90
-120.91
-120.93
-120.93
-125.78
-125.79
-125.80
-125.81
-125.83
-125.84
-125.85
-125.86
-125.87
-125.87
-125.88
ONf
Chemical Formula: C11H5F9O5S
Exact Mass: 419.9714
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

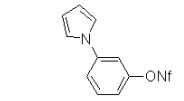

7.27
7.25
7.23
6.69
6.68
6.67
6.66
6.61
6.60
6.59
6.58
6.54
6.53
6.53
2.98
Me2N
ONf
Chemical Formula: C12H10F9NO3S
Exact Mass: 419.0238
1.03
1.00
1.01
0.99
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


151.93
151.20
130.35
111.84
108.14
104.69
77.48
77.16
76.84
40.40
Me2N
ONf
Chemical Formula: C12H10F9NO3S
Exact Mass: 419.0238
f1 (ppm)

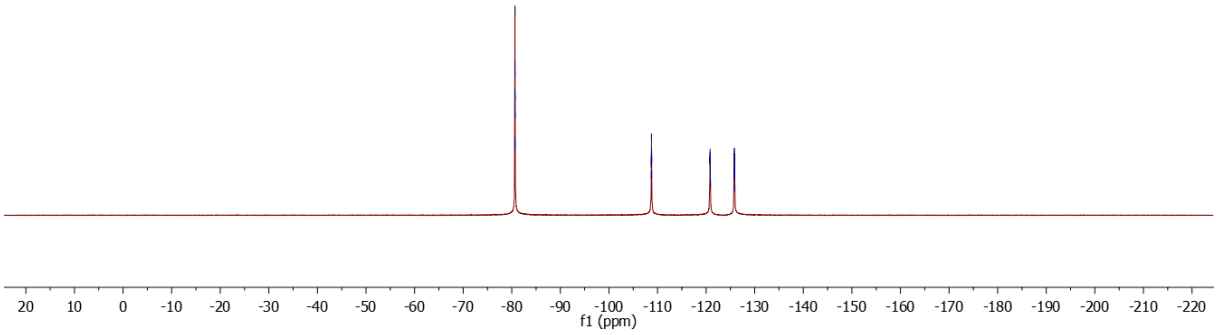

Me2N
ONf
Chemical Formula: C12H10F9NO3S
Exact Mass: 419.0238
f1 (ppm)

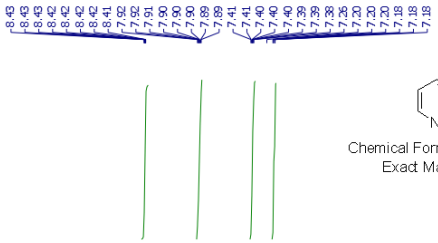

7.53
7.51
7.49
7.44
7.44
7.44
7.42
7.42
7.42
7.42
7.33
7.32
7.31
7.25
7.18
7.18
7.16
7.16
7.10
7.09
7.09
6.40
6.40
6.39
ONf
Chemical Formula: C14H6F9NO3S
Exact Mass: 441.0081
1.07
1.08
1.04
1.06
2.12
2.00
f1 (ppm)


150.43
142.43
131.27
120.00
119.33
118.08
113.59
111.75
77.48
77.16
76.84
ONf
Chemical Formula: C14H8F9NO3S
Exact Mass: 441.0081
f1 (ppm)

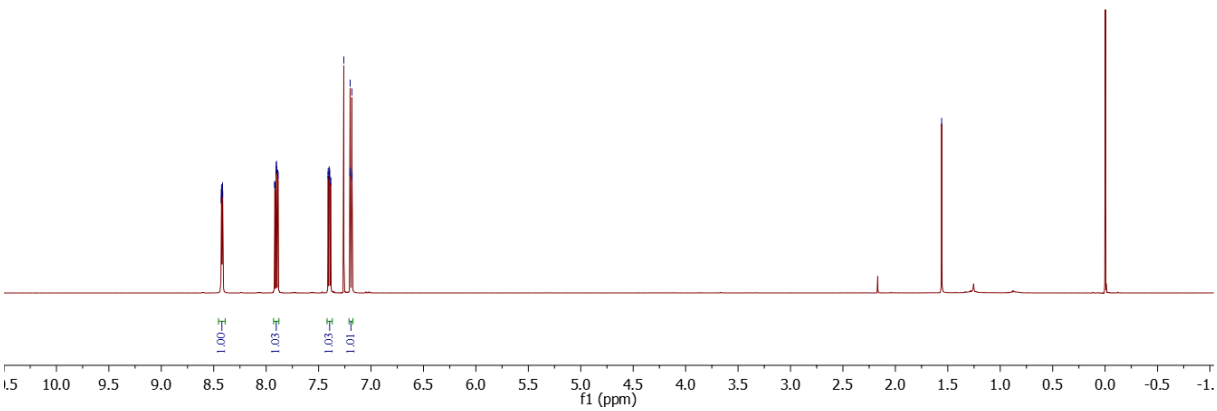


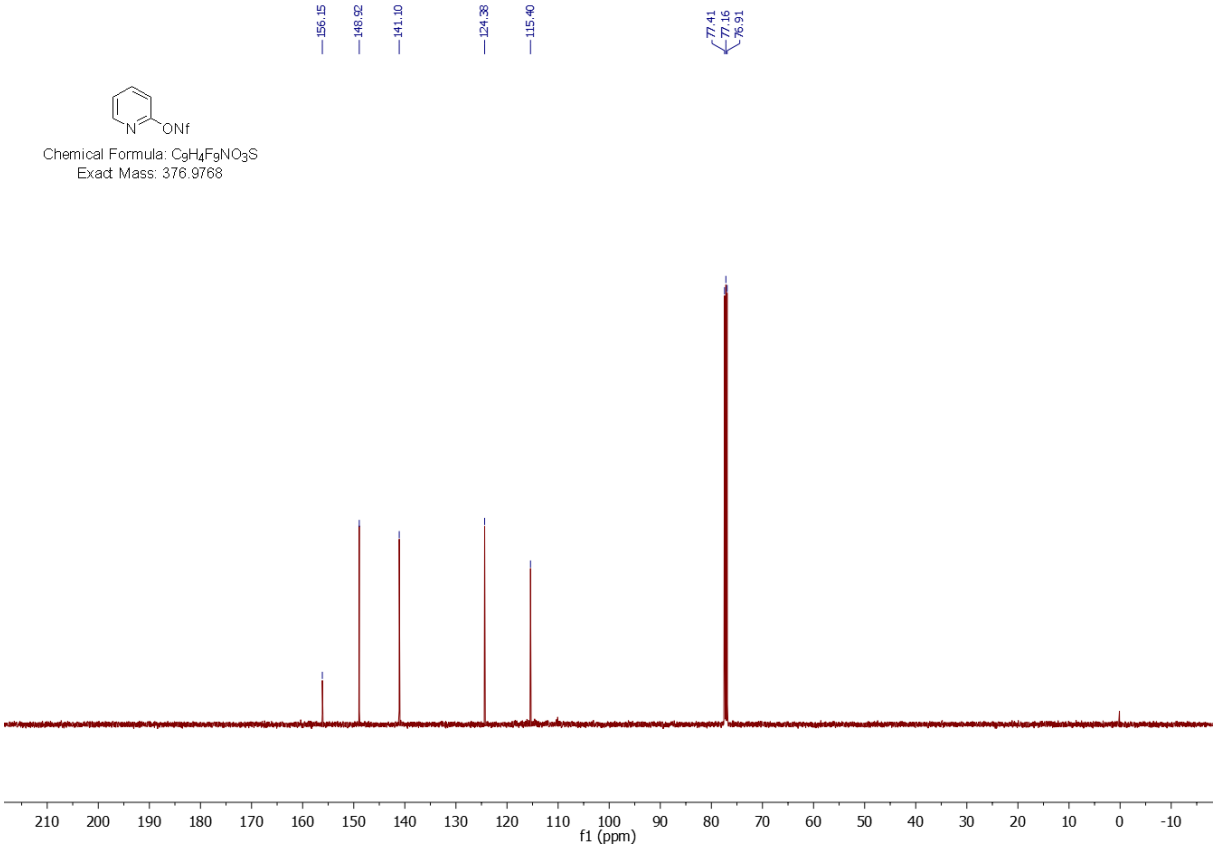
Chemical Formula: $C_{14}H_8F_9NO_3S$
Exact Mass: 441.0081

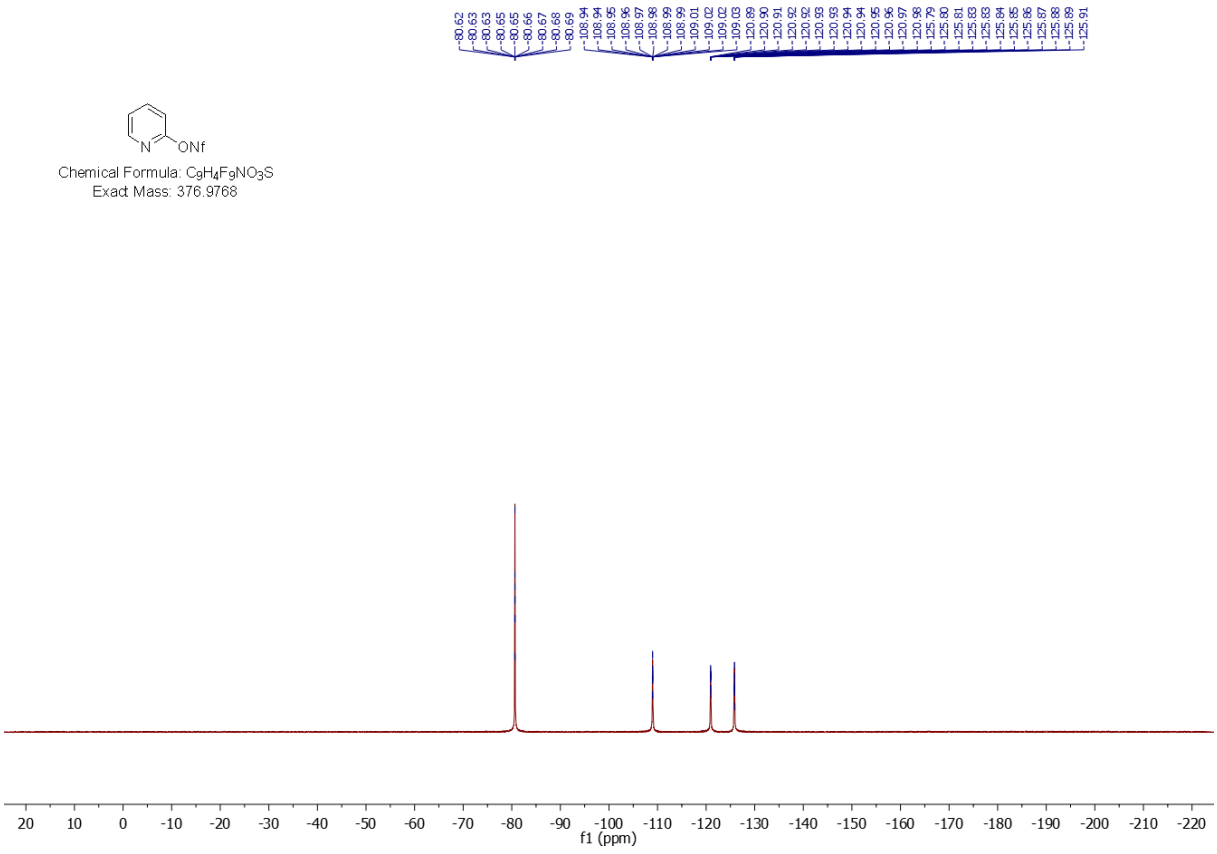


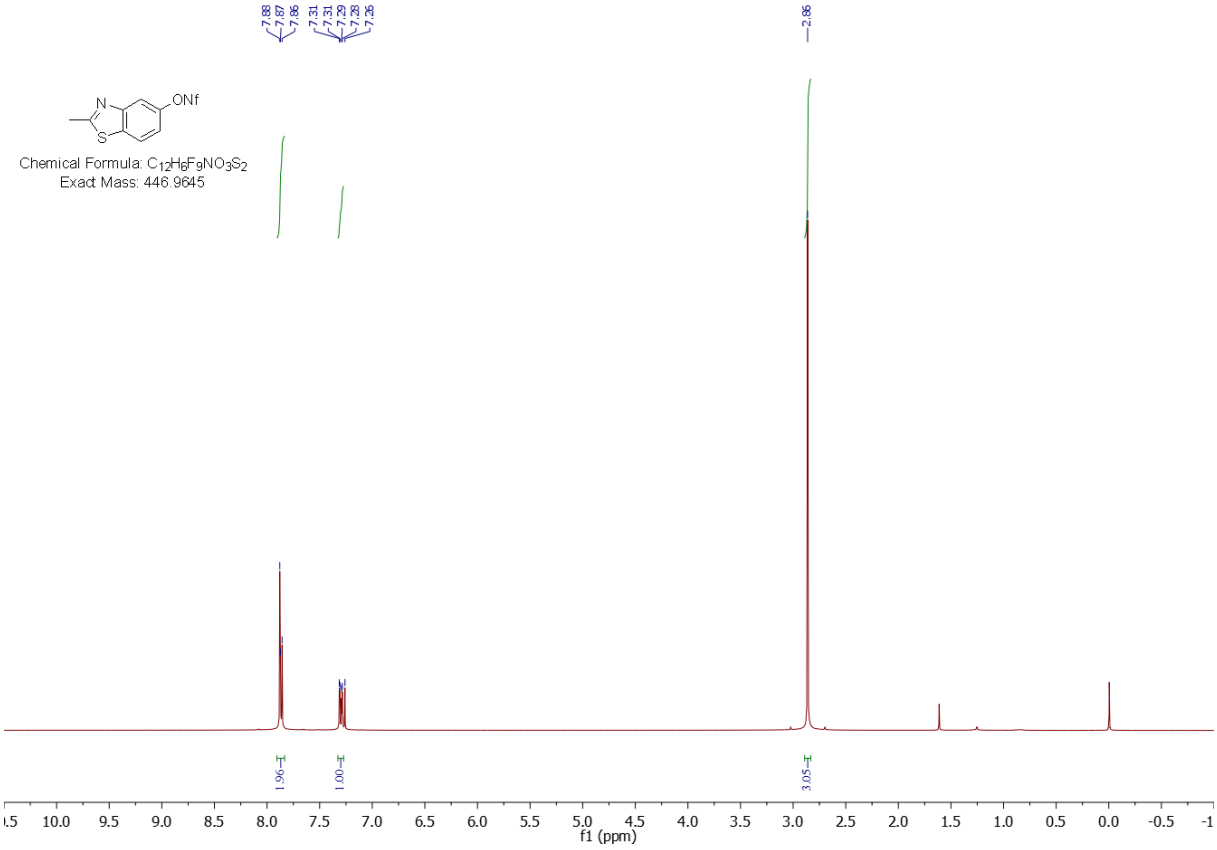


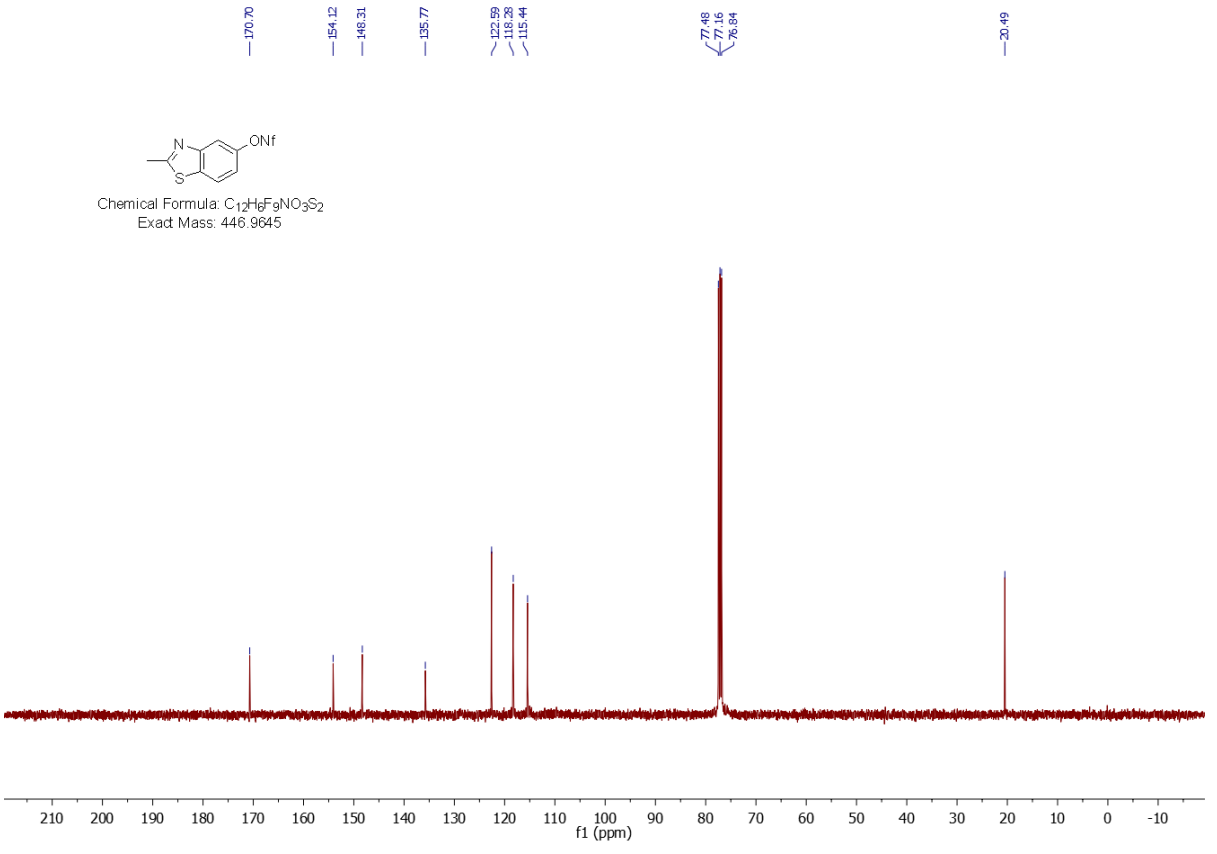
Chemical Formula: $C_9H_4F_9NO_3S$
Exact Mass: 376.9768

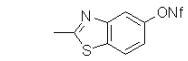



156.15
148.92
141.10
124.38
115.40
77.41
77.16
76.91
ONf
Chemical Formula: C9H4F9NO3S
Exact Mass: 376.9768
f1 (ppm)

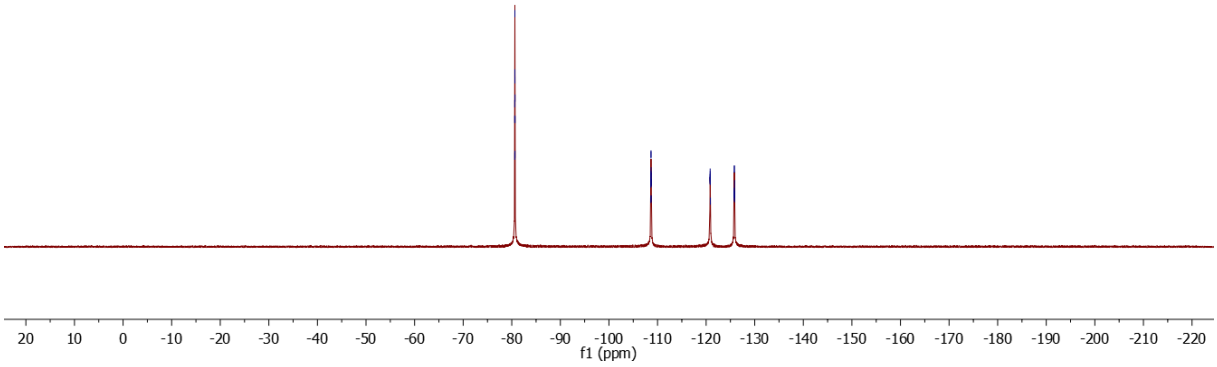

ONf
Chemical Formula: C9H4F9NO3S
Exact Mass: 376.9768
f1 (ppm)

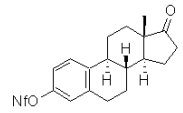

7.88
7.87
7.86
7.31
7.31
7.29
7.28
7.26
2.86
ONf
Chemical Formula: C12H6F9NO3S2
Exact Mass: 446.9645
1.96
1.00
3.05
f1 (ppm)


170.70
154.12
148.31
135.77
122.59
118.28
115.44
77.48
77.16
76.84
20.49
ONf
Chemical Formula: C12H6F9NO3S2
Exact Mass: 446.9645
f1 (ppm)

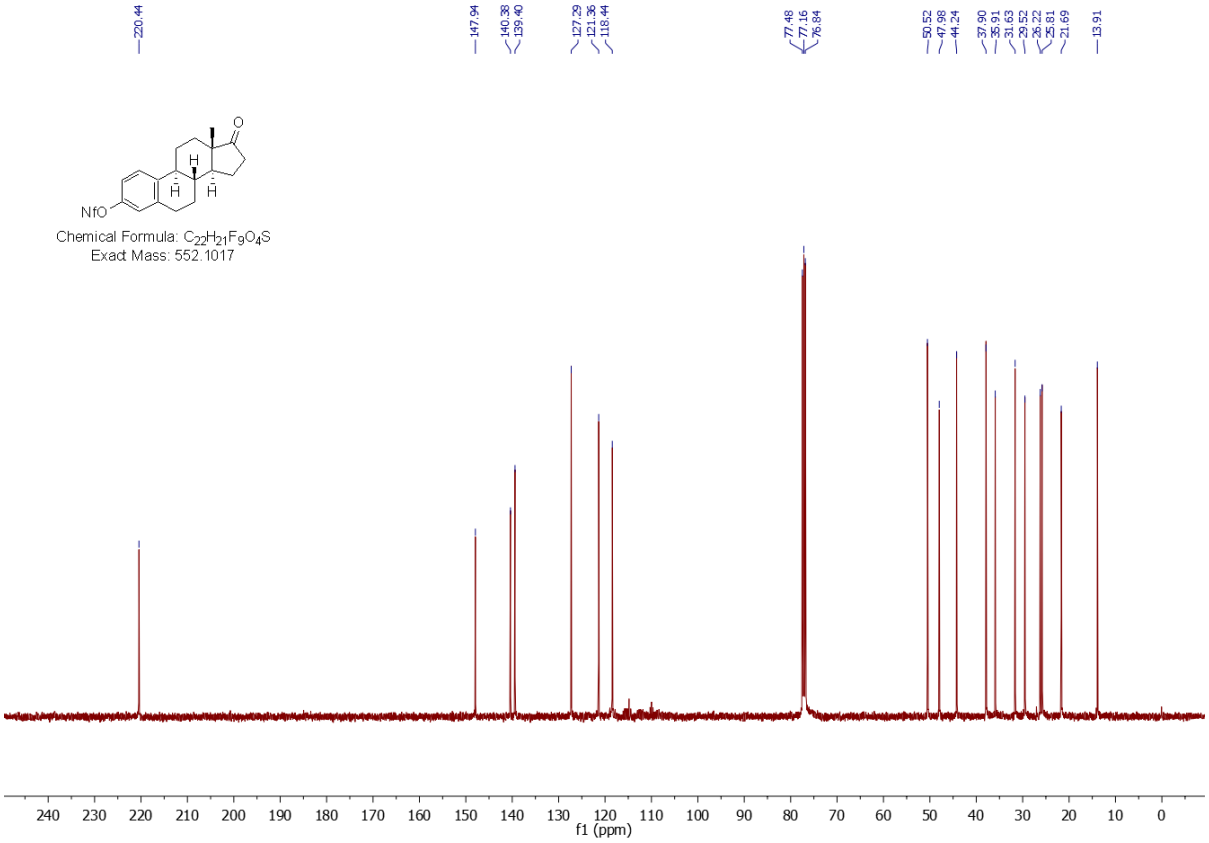


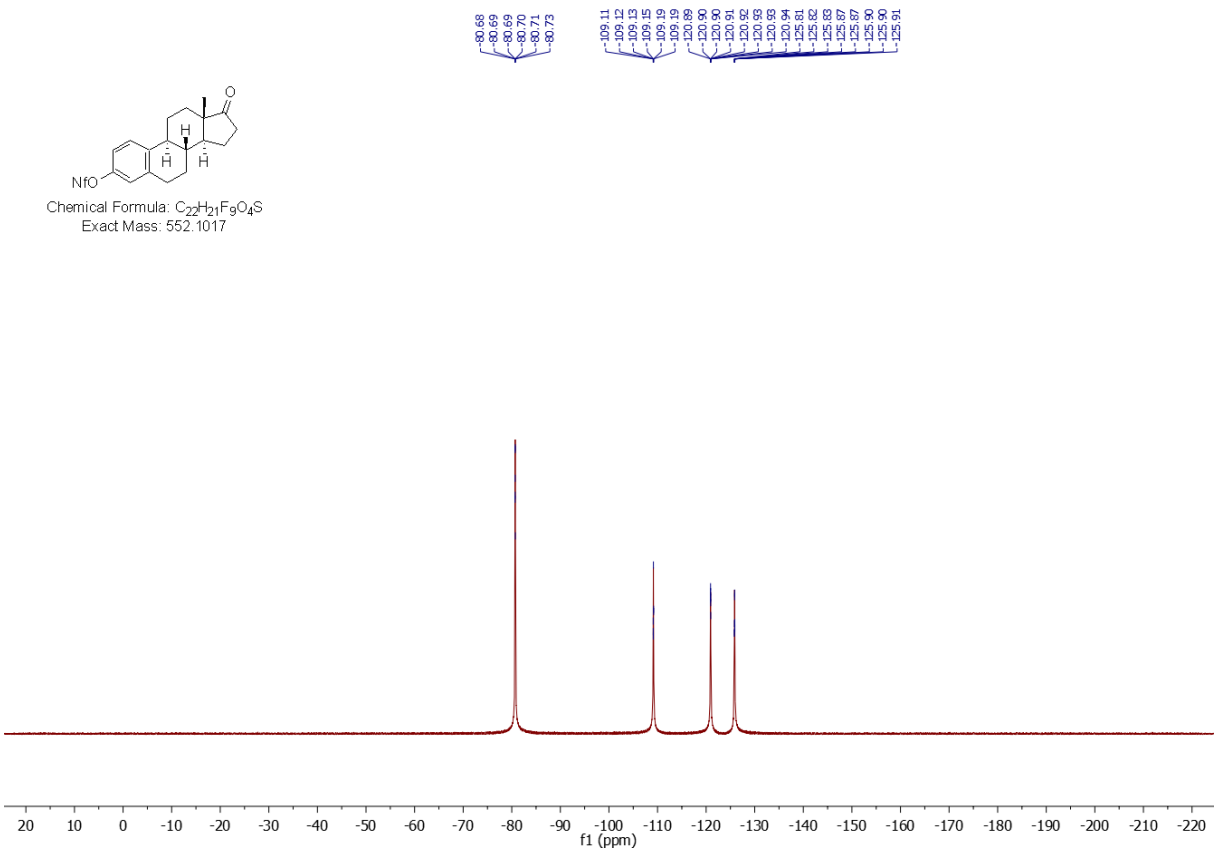
Chemical Formula: $C_{12}H_6F_9NO_3S_2$
Exact Mass: 446.9645

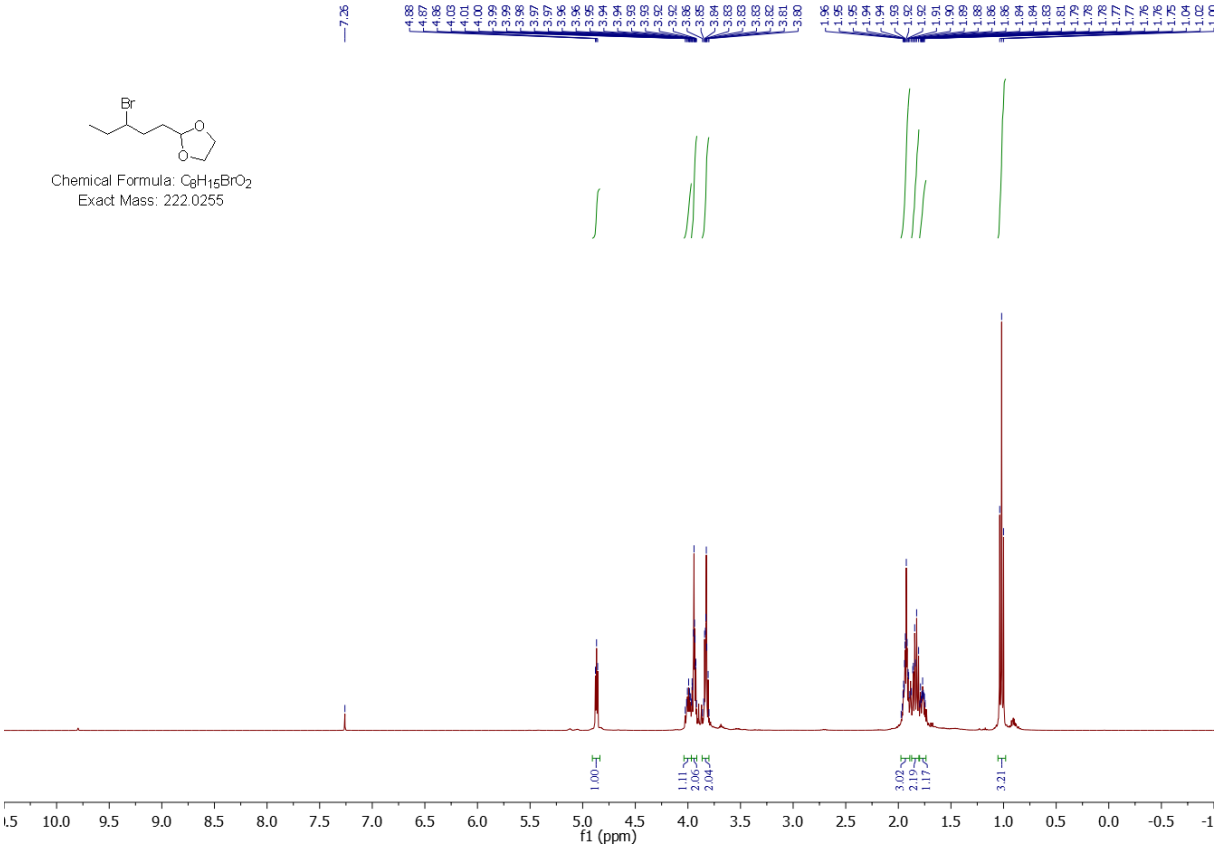


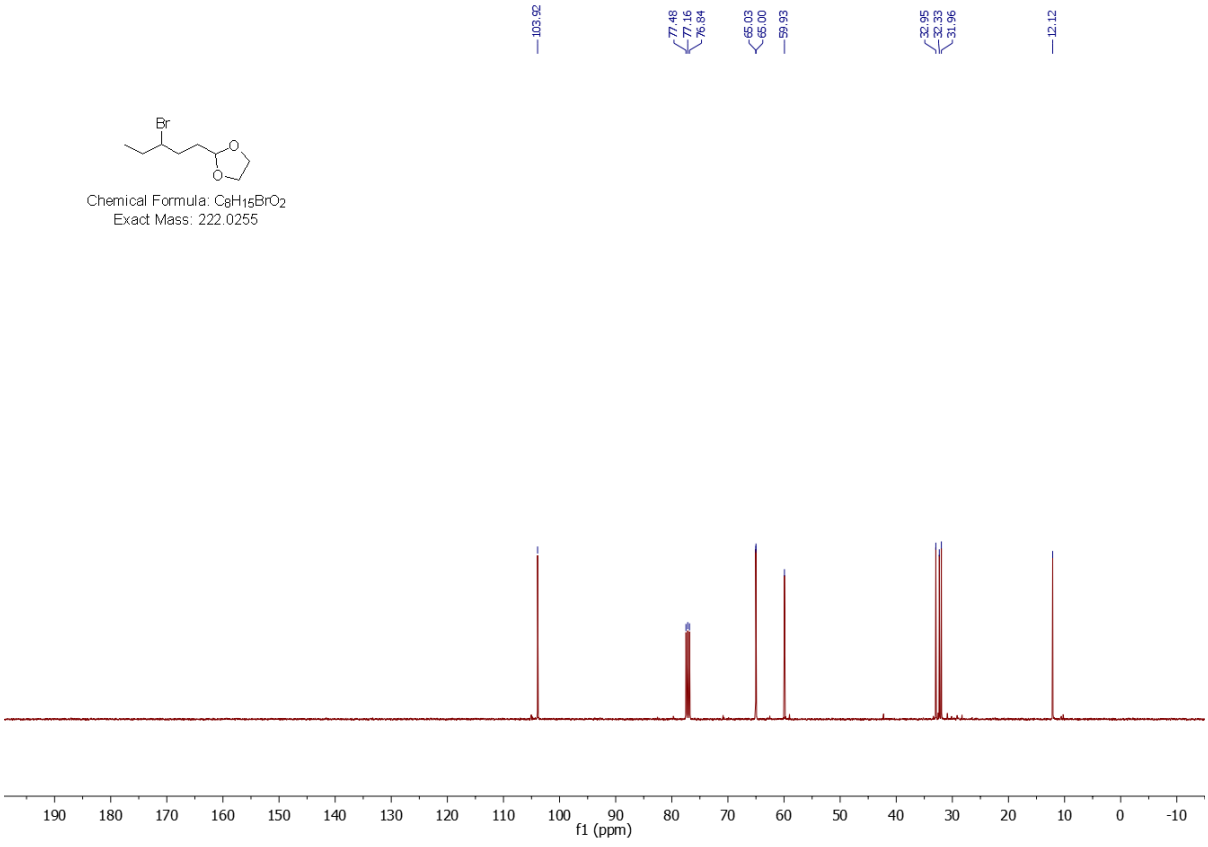


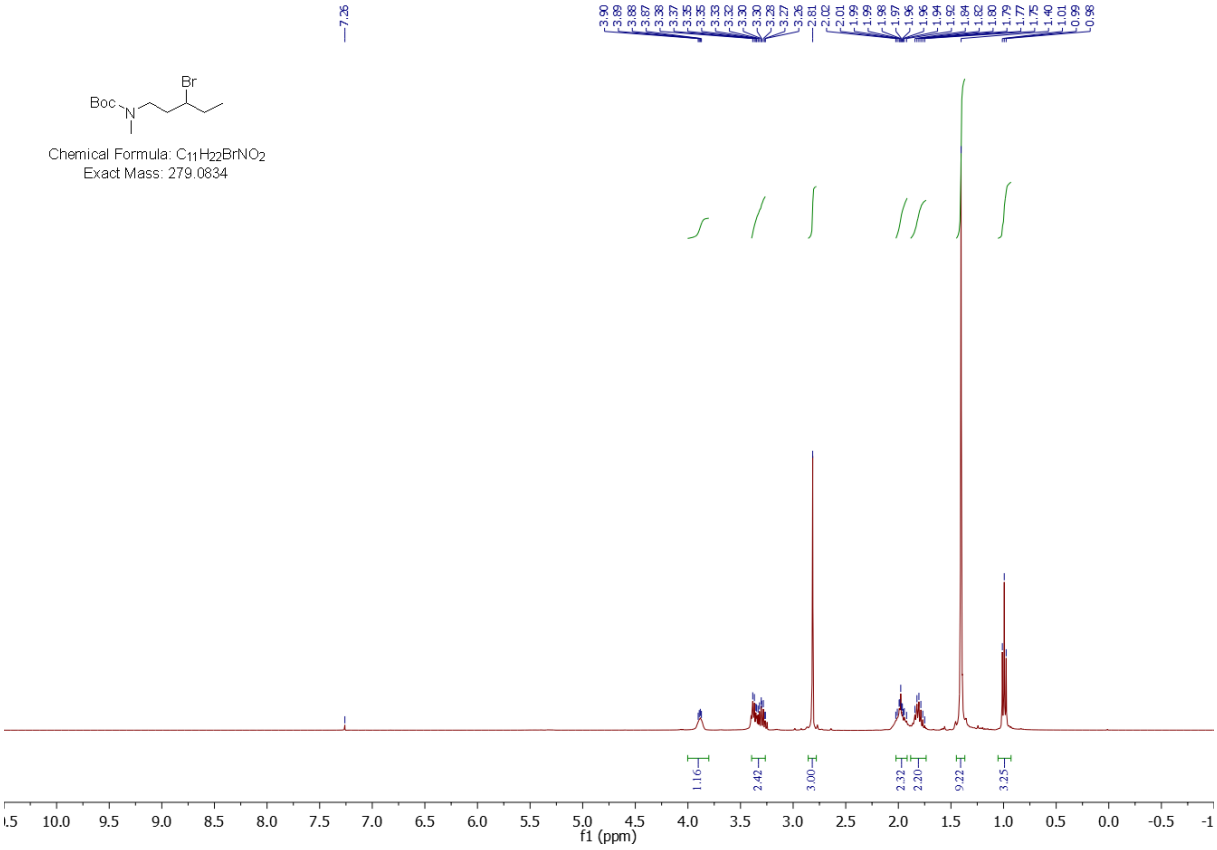
Chemical Formula: $C_{22}H_{21}F_9O_4S$
Exact Mass: 552.1017

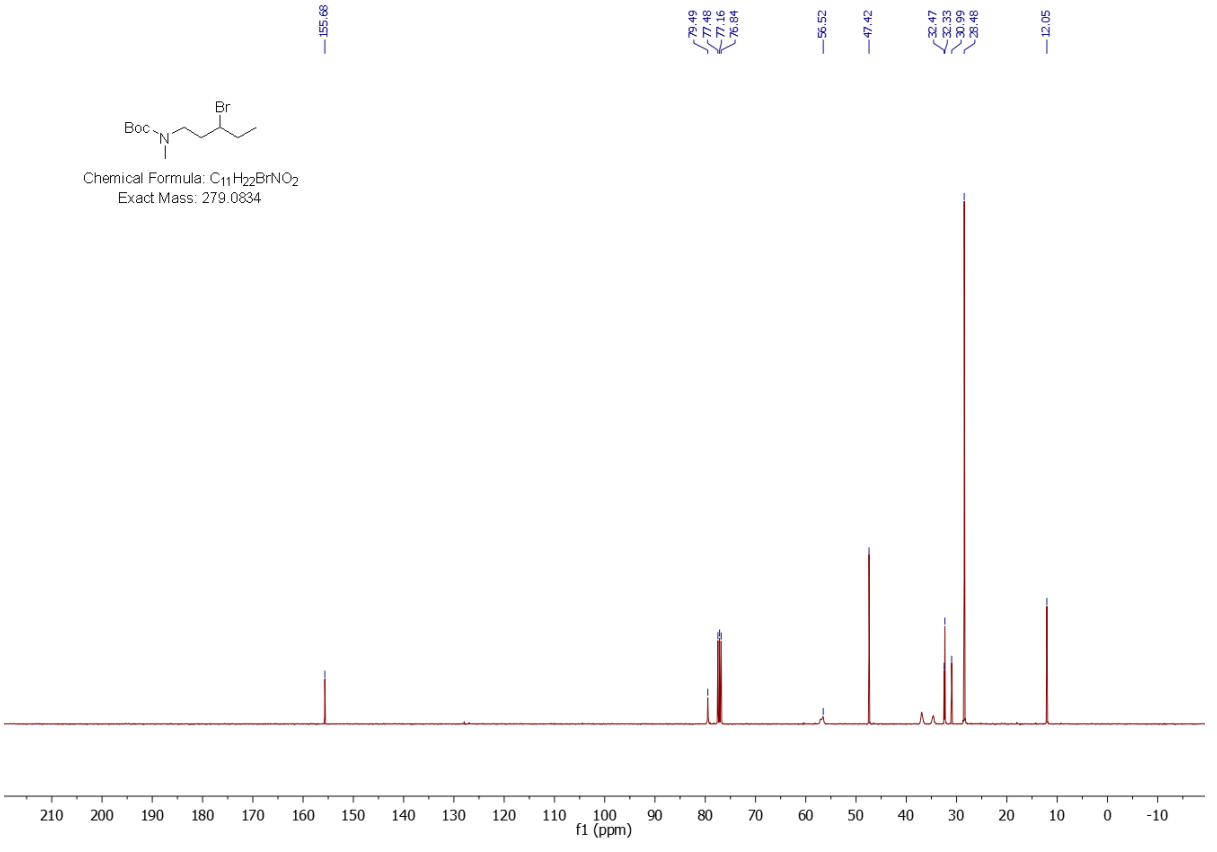

220.44
147.94
140.38
139.40
127.29
121.36
118.44
77.48
77.16
76.84
50.52
47.98
44.24
37.90
35.91
31.63
29.52
26.22
25.81
21.69
13.91
O
H
H
H
NfO
Chemical Formula: C22H21F9O4S
Exact Mass: 552.1017
240 230 220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

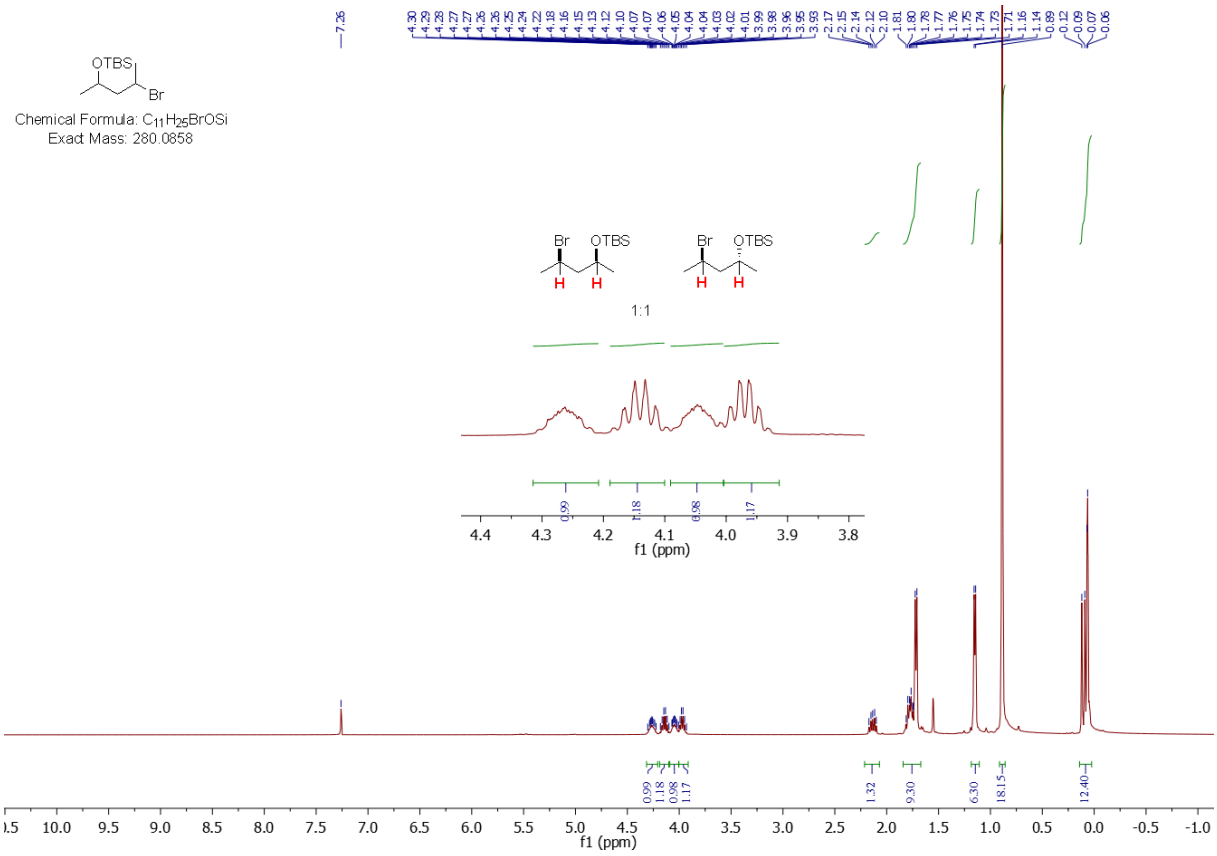

80.68
80.69
80.69
80.70
80.71
80.73
109.11
109.12
109.13
109.15
109.19
109.19
120.89
120.90
120.90
120.91
120.92
120.93
120.93
120.94
125.81
125.82
125.83
125.87
125.87
125.90
125.90
125.91
O
H
H
H
NfO
Chemical Formula: C22H21F9O4S
Exact Mass: 552.1017
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

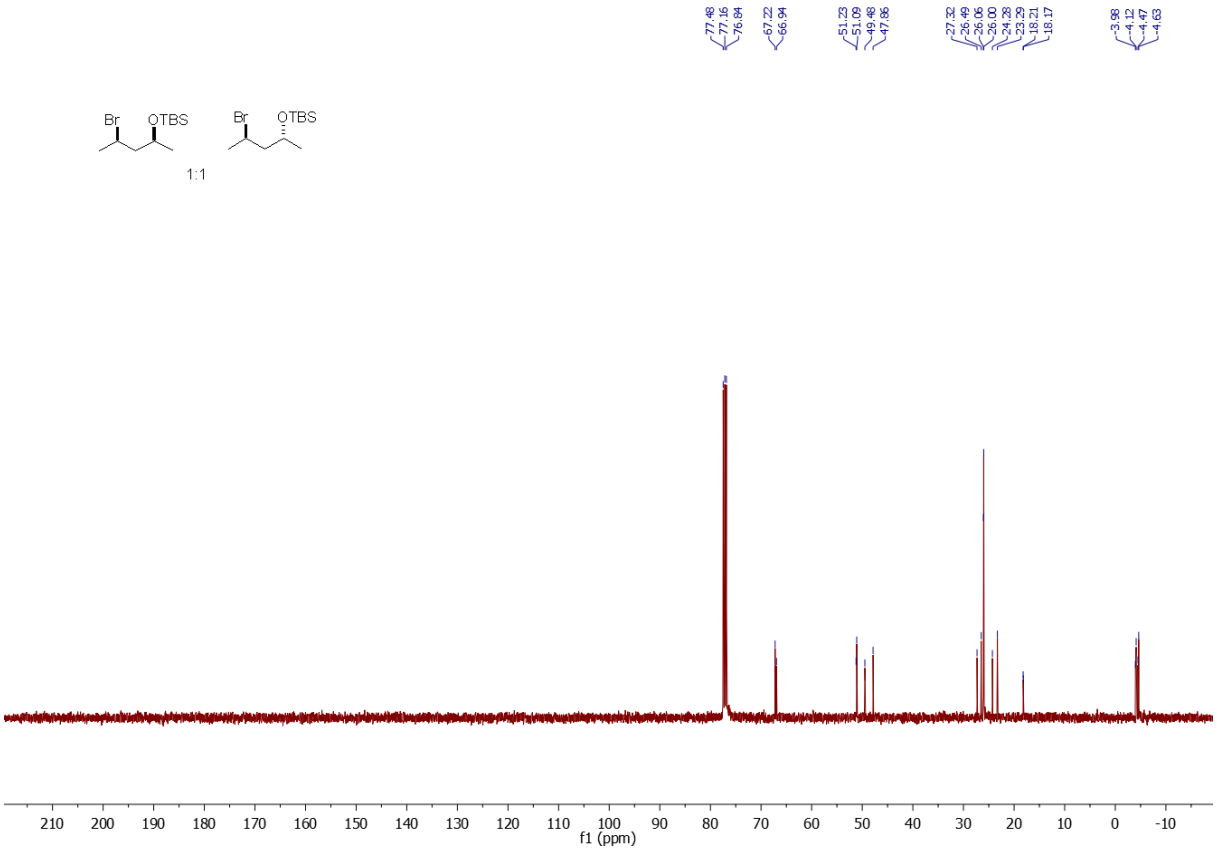

Br
Chemical Formula: C8H15BrO2
Exact Mass: 222.0255
f1 (ppm)

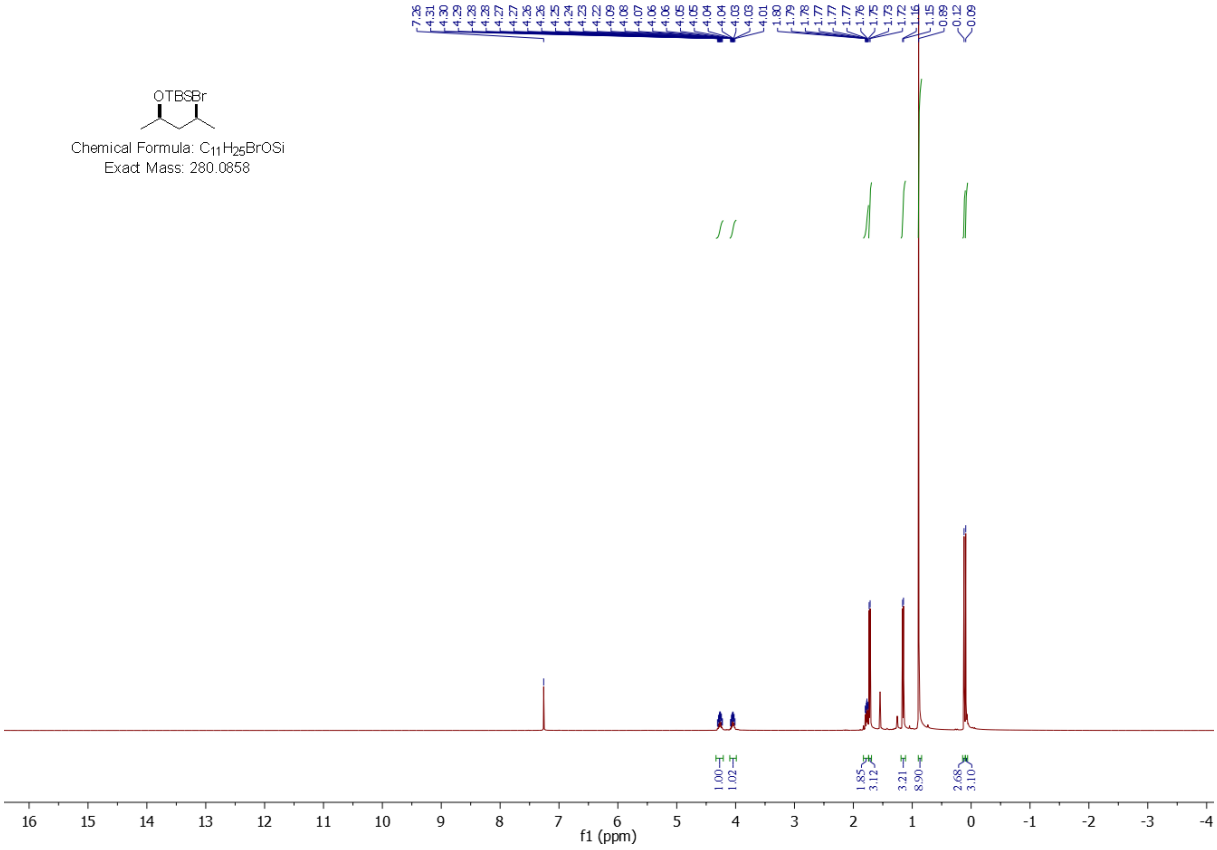

Br
Chemical Formula: C8H15BrO2
Exact Mass: 222.0255
f1 (ppm)

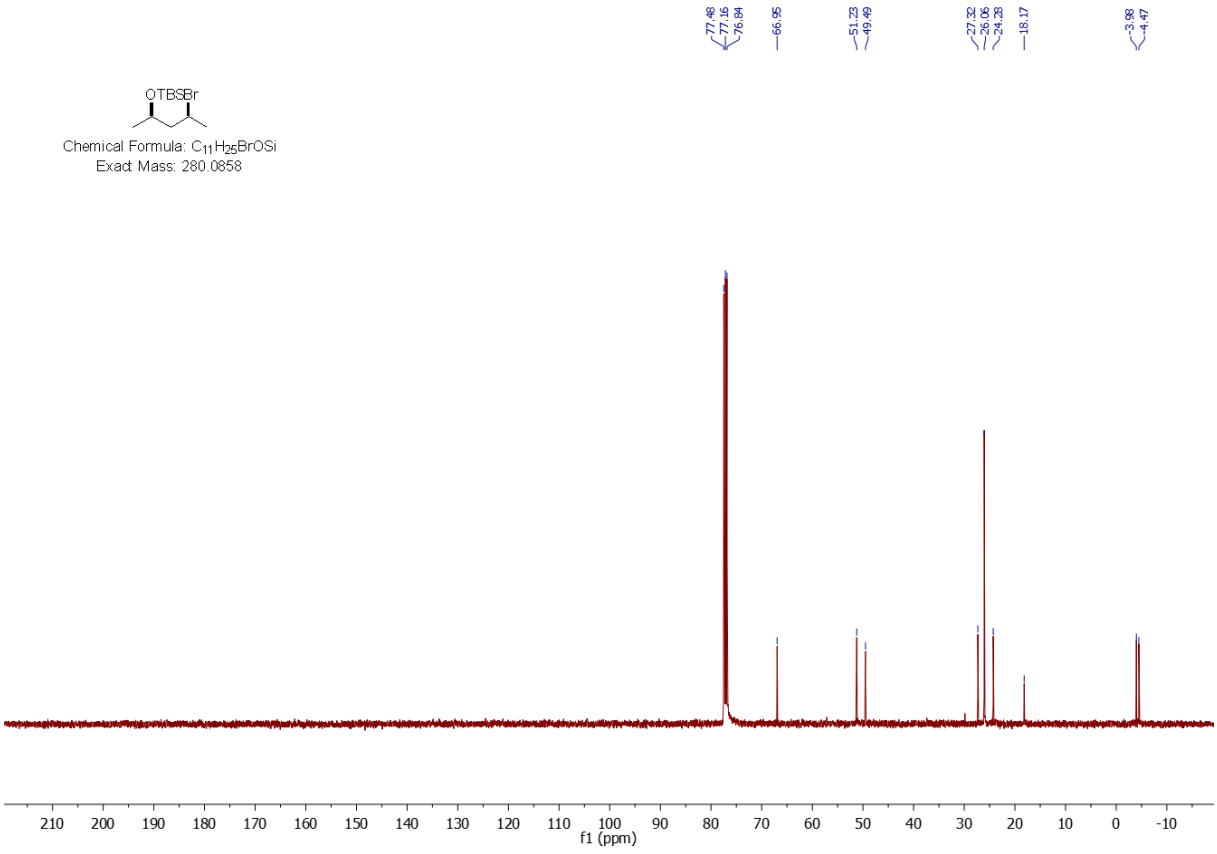

Br
Boc
N
Chemical Formula: C11H22BrNO2
Exact Mass: 279.0834
7.26
3.90
3.89
3.88
3.87
3.38
3.37
3.35
3.35
3.33
3.32
3.30
3.30
3.28
3.27
3.26
2.81
2.02
2.01
1.99
1.99
1.98
1.97
1.96
1.96
1.94
1.92
1.84
1.82
1.80
1.79
1.77
1.75
1.40
1.01
0.99
0.98
1.16
2.42
3.00
2.32
2.20
9.22
3.25
f1 (ppm)

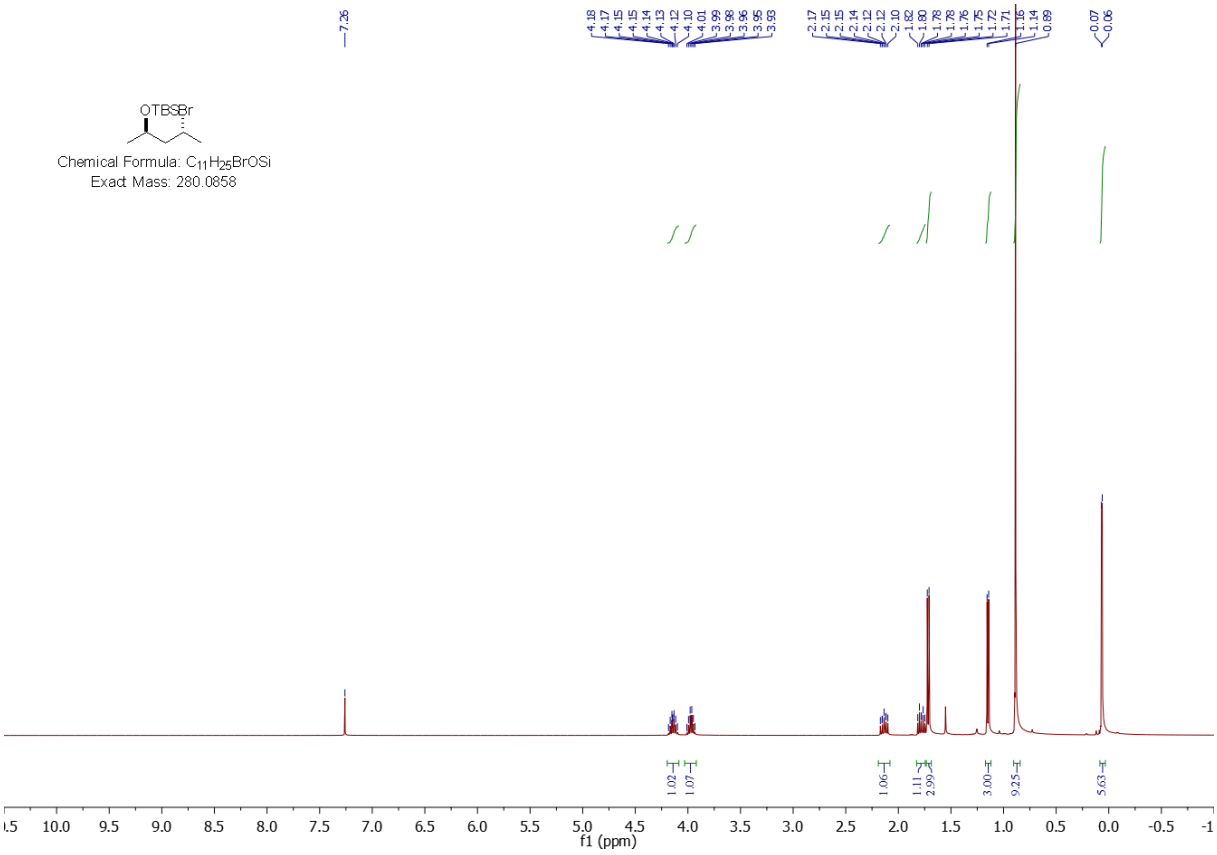

Br
Boc
N
Chemical Formula: C11H22BrNO2
Exact Mass: 279.0834
155.68
79.49
77.48
77.16
76.84
56.52
47.42
32.47
32.33
30.99
28.48
12.05
f1 (ppm)

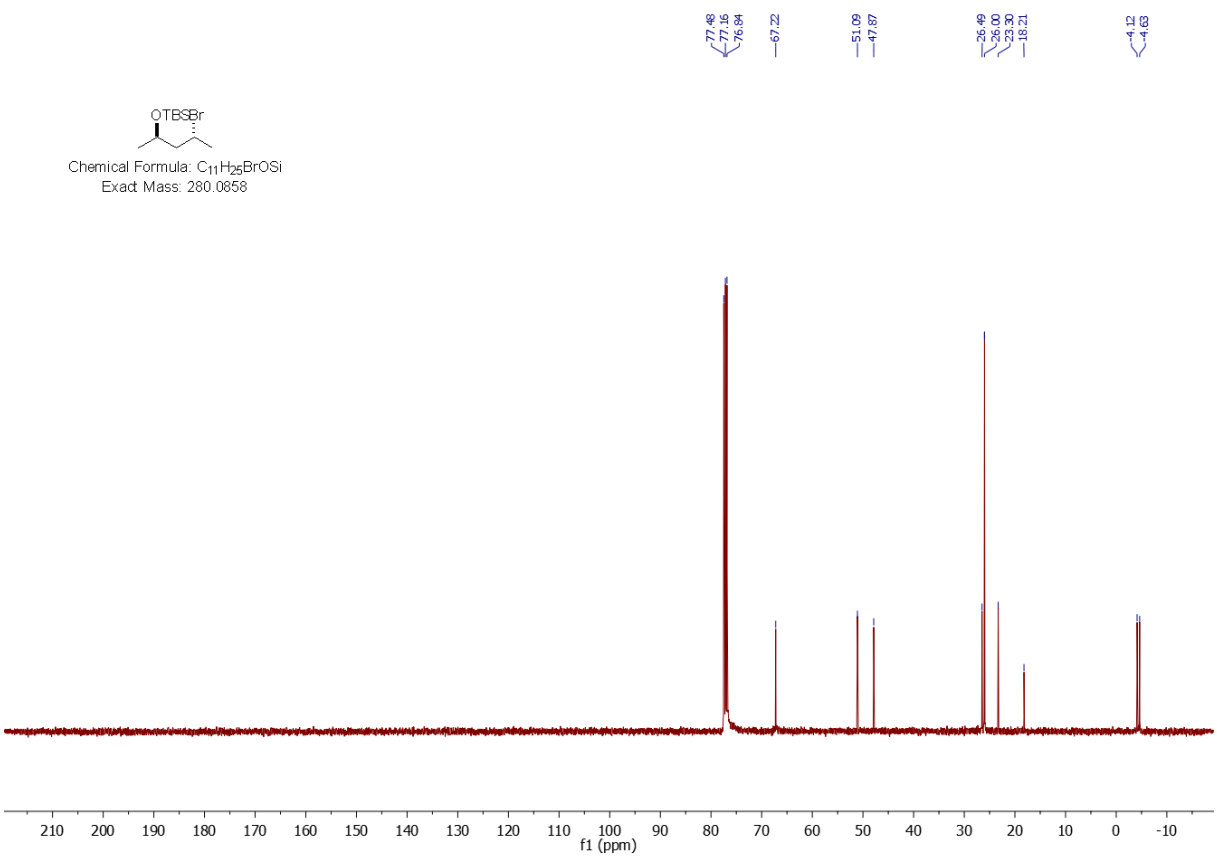

OTBS
Br
Chemical Formula: C11H25BrOSi
Exact Mass: 280.0858
Br OTBS
H H
Br OTBS
H H
1:1
f1 (ppm)
f1 (ppm)

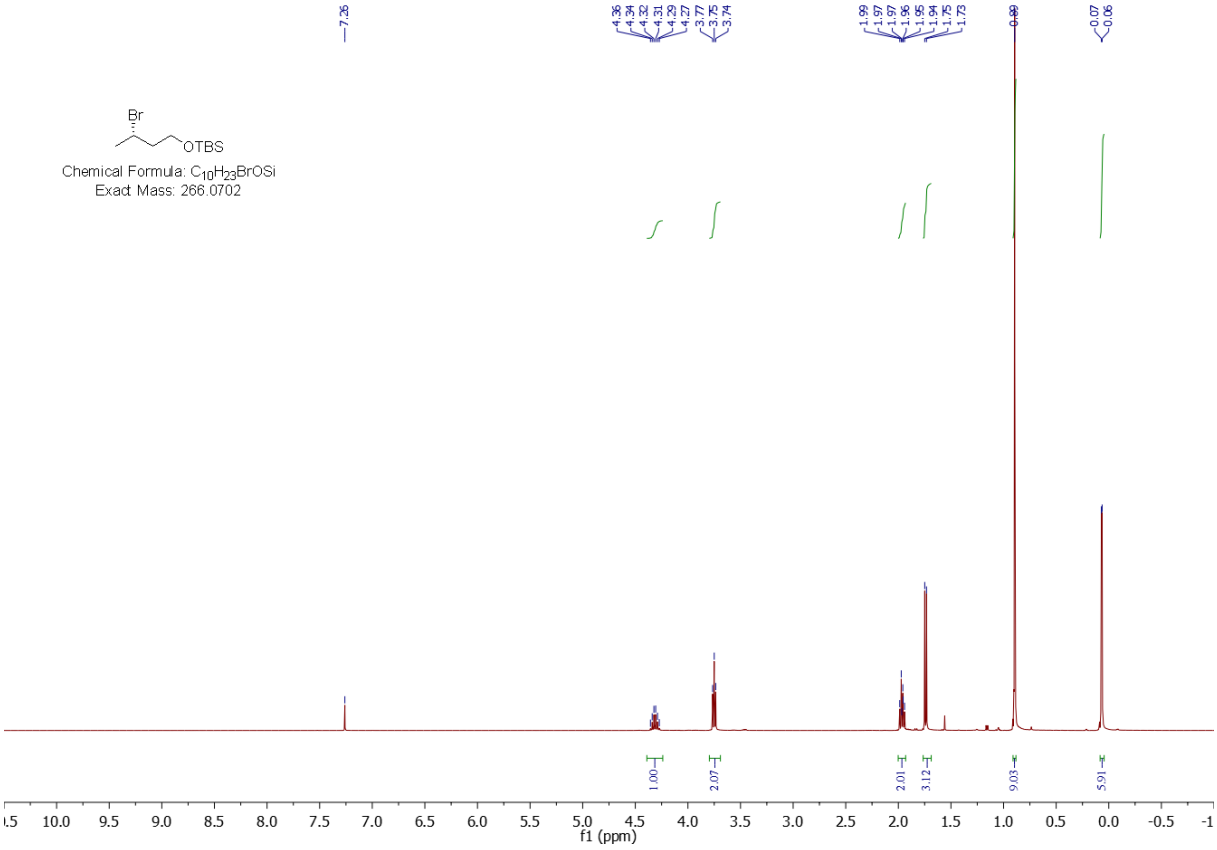

Br OTBS
Br OTBS
1:1
f1 (ppm)

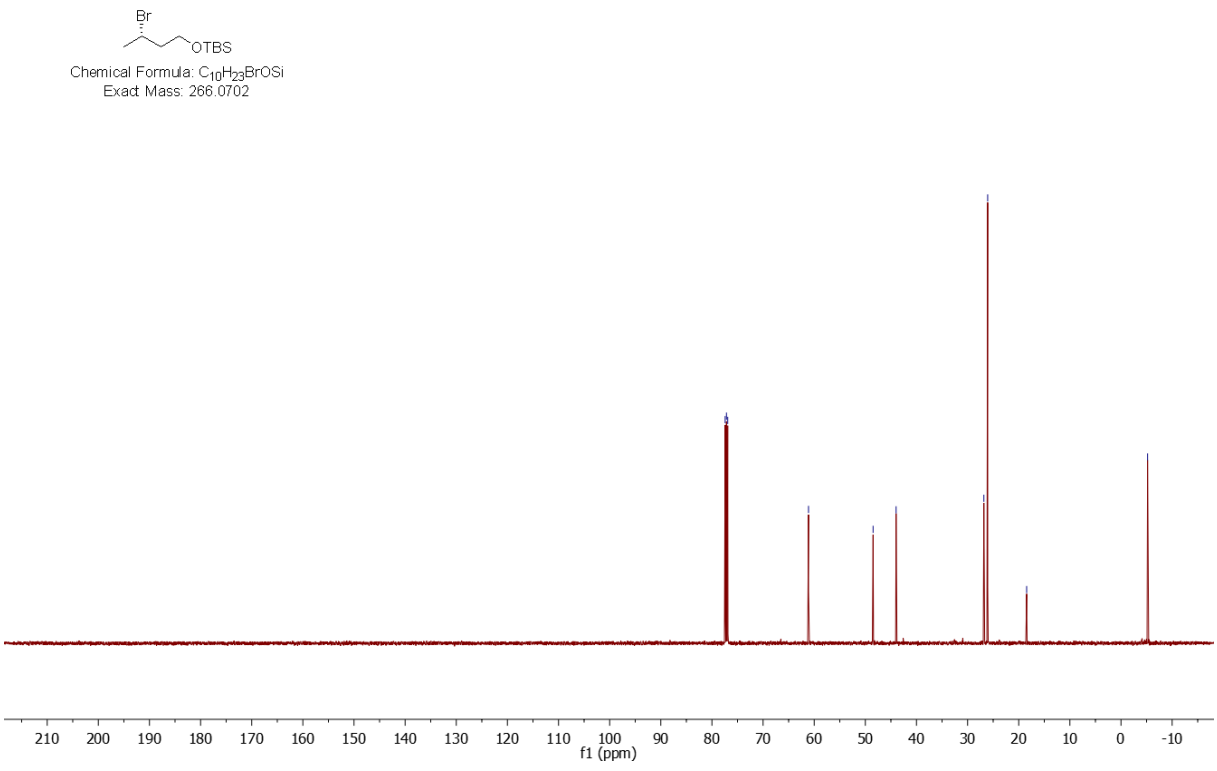

OTBSBr
Chemical Formula: C11H25BrOSi
Exact Mass: 280.0858
f1 (ppm)

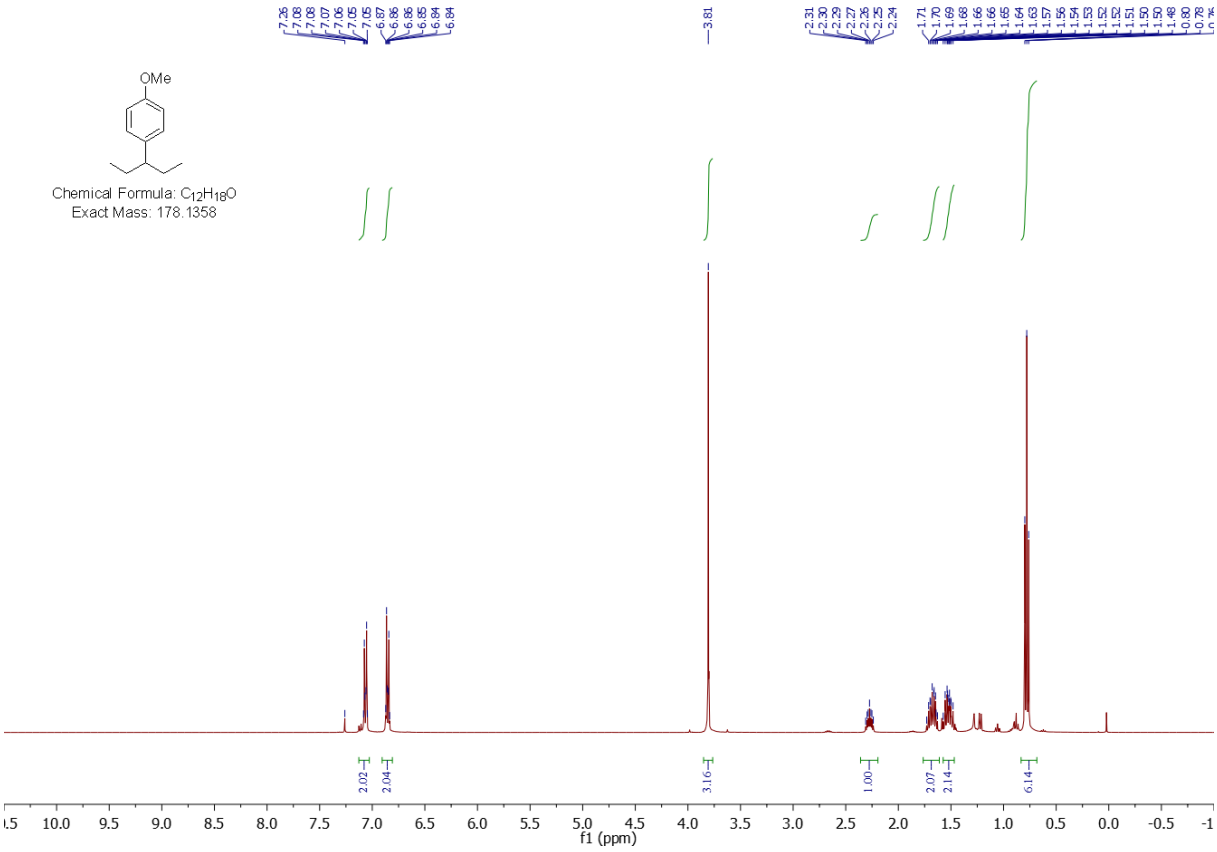

OTBSBr
Chemical Formula: C11H25BrOSi
Exact Mass: 280.0858
f1 (ppm)

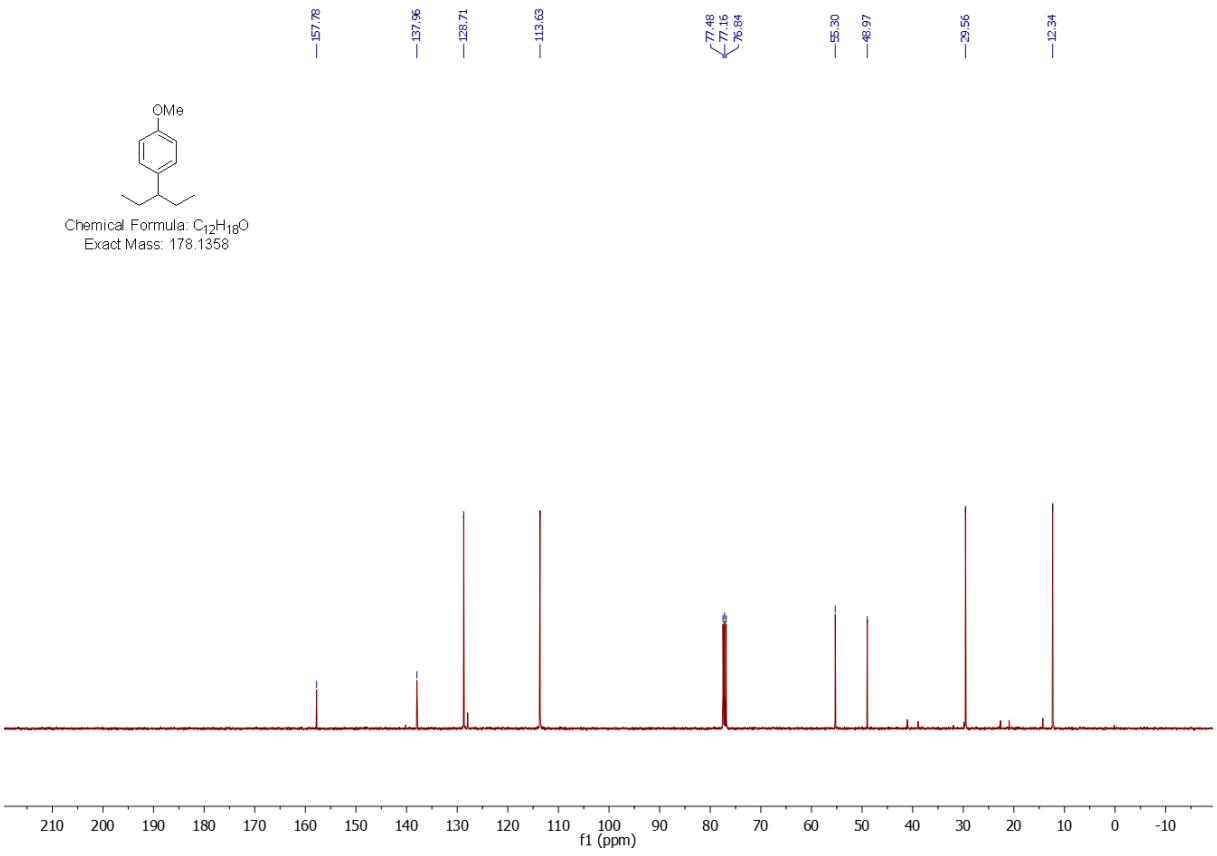

OTBSBr
Chemical Formula: C11H25BrOSi
Exact Mass: 280.0858
f1 (ppm)

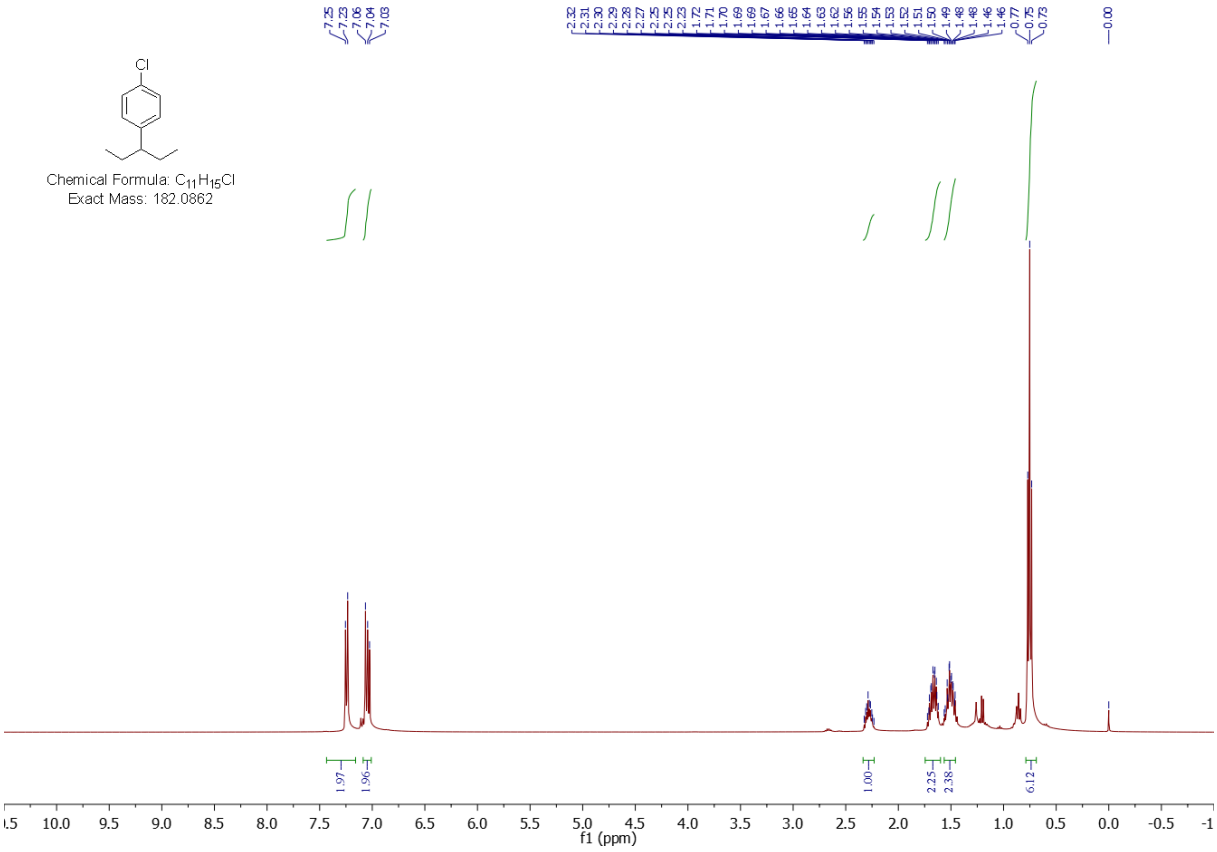

OTBSBr
Chemical Formula: C11H25BrOSi
Exact Mass: 280.0858
f1 (ppm)

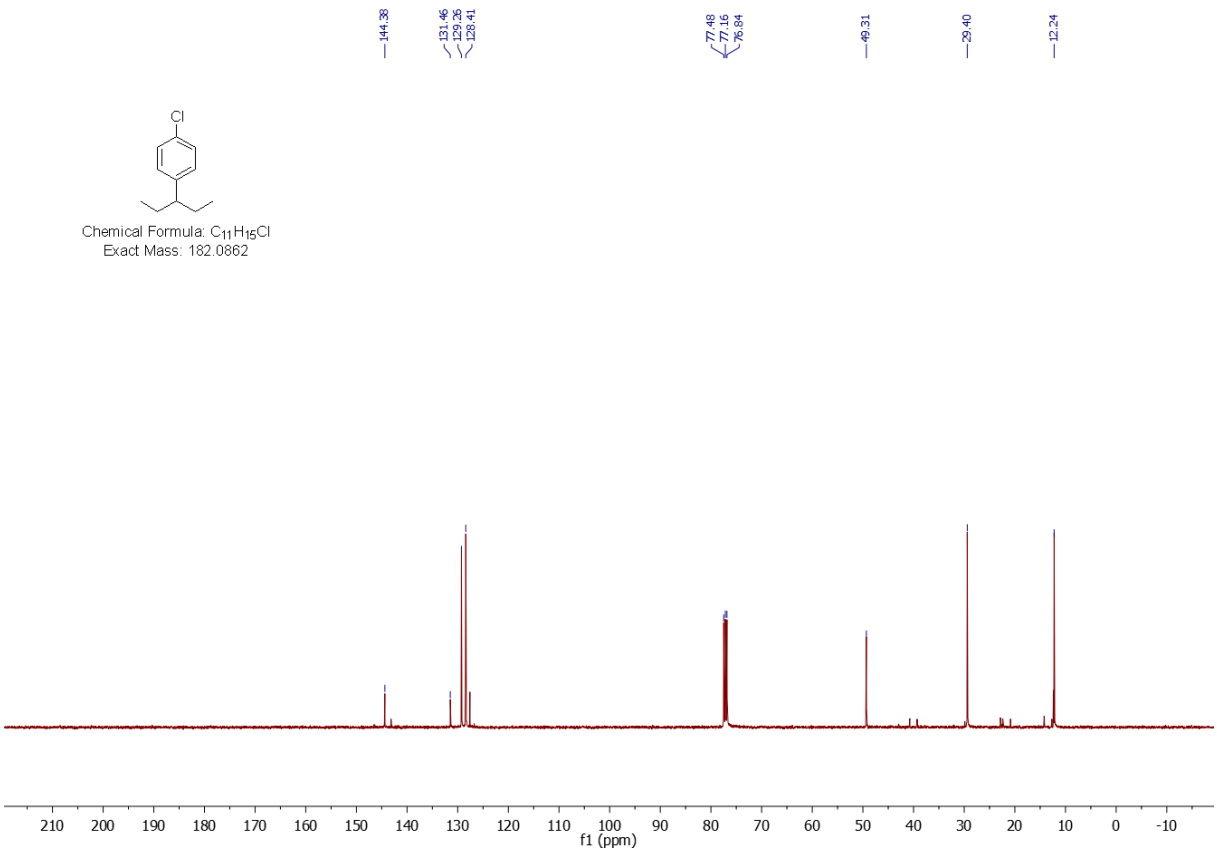

Br
OTBS
Chemical Formula: C10H23BrOSi
Exact Mass: 266.0702
7.26
4.36
4.34
4.32
4.31
4.29
4.27
3.77
3.75
3.74
1.99
1.97
1.97
1.96
1.95
1.94
1.75
1.73
0.89
0.07
0.06
1.00
2.07
2.01
3.12
9.03
5.91
f1 (ppm)

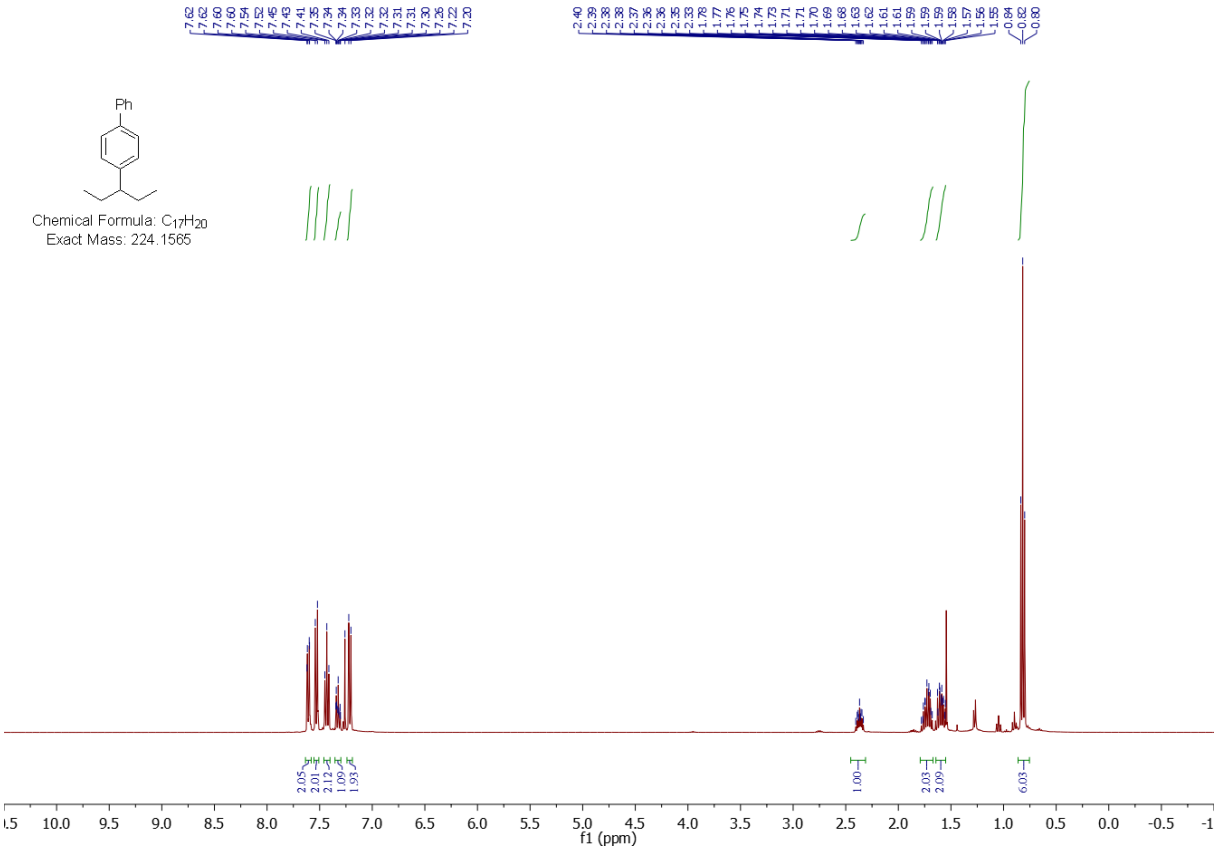

Br
OTBS
Chemical Formula: C10H23BrOSi
Exact Mass: 266.0702
77.41
77.16
76.91
61.11
48.48
43.98
26.82
26.07
18.45
-5.20
f1 (ppm)

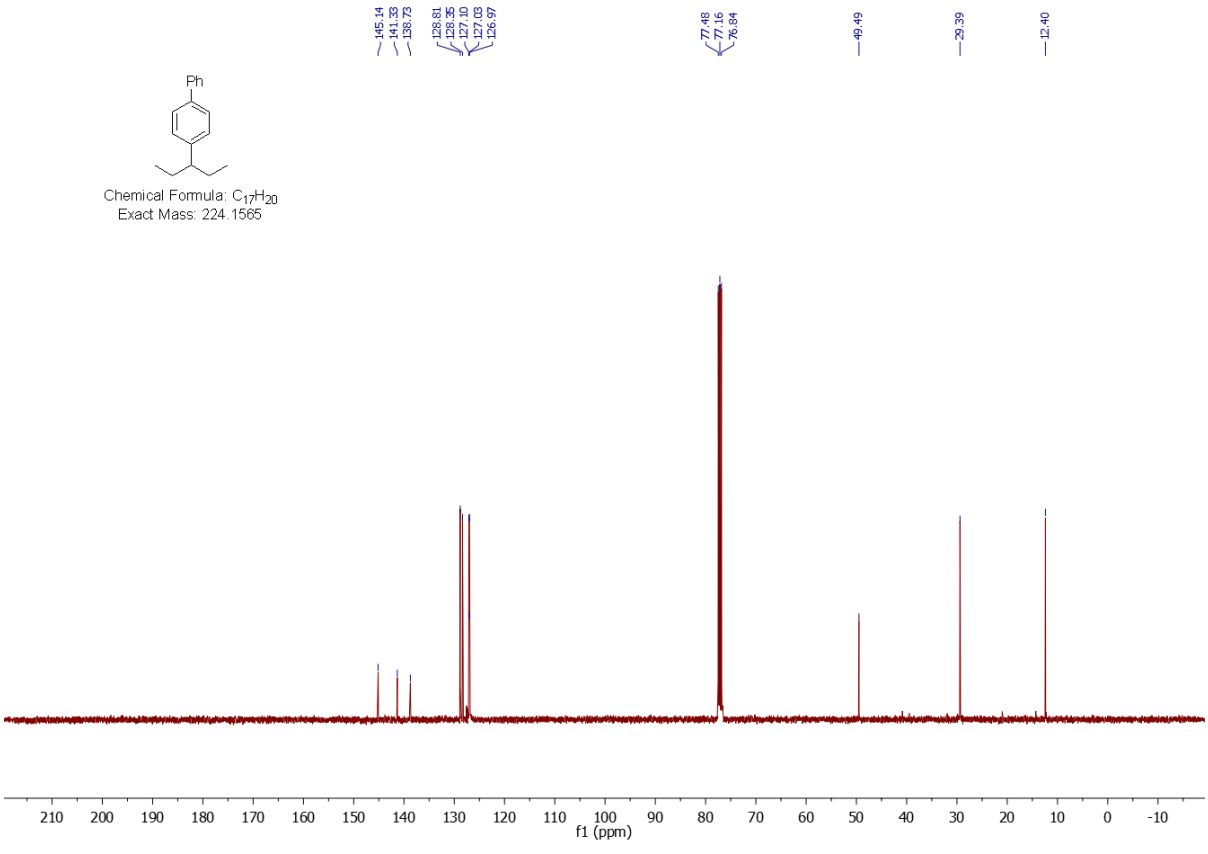

OMe
Chemical Formula: C12H18O
Exact Mass: 178.1358
f1 (ppm)

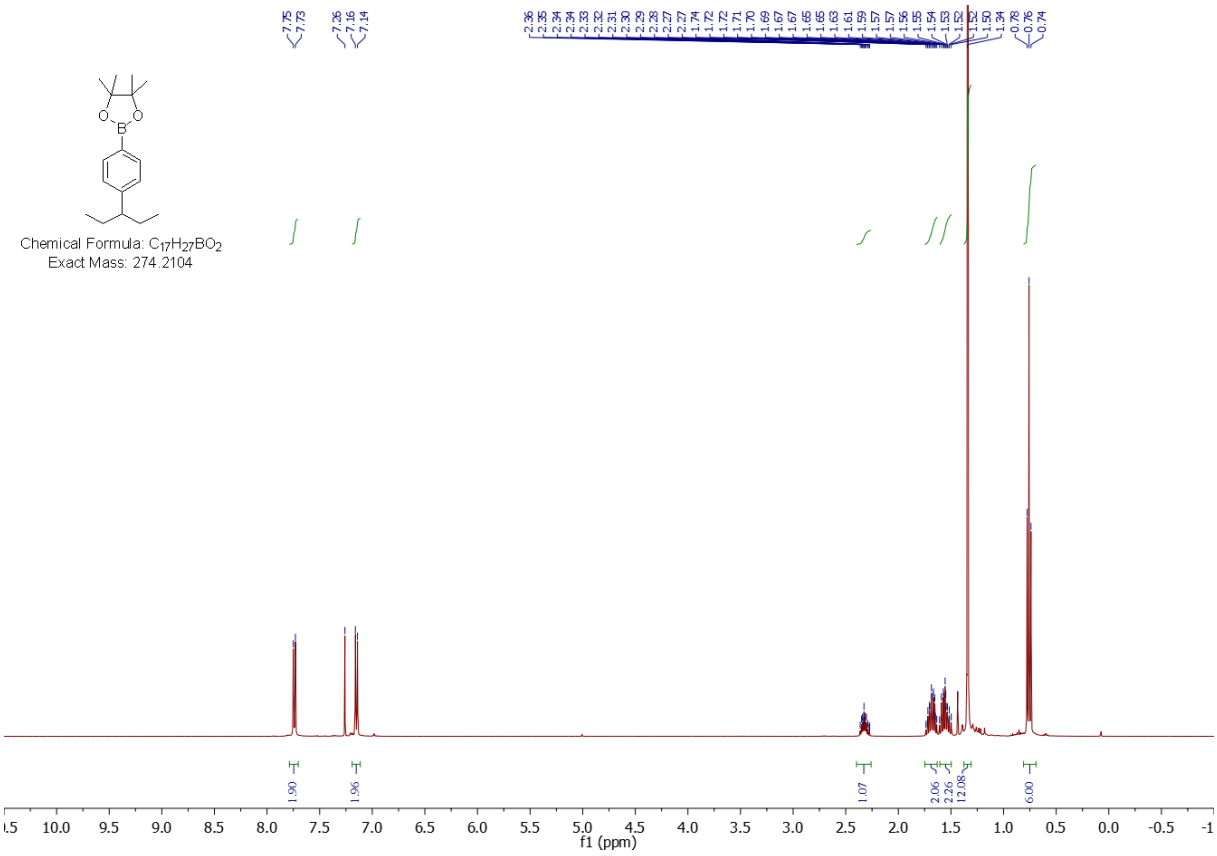

OMe
Chemical Formula: C12H18O
Exact Mass: 178.1358
f1 (ppm)

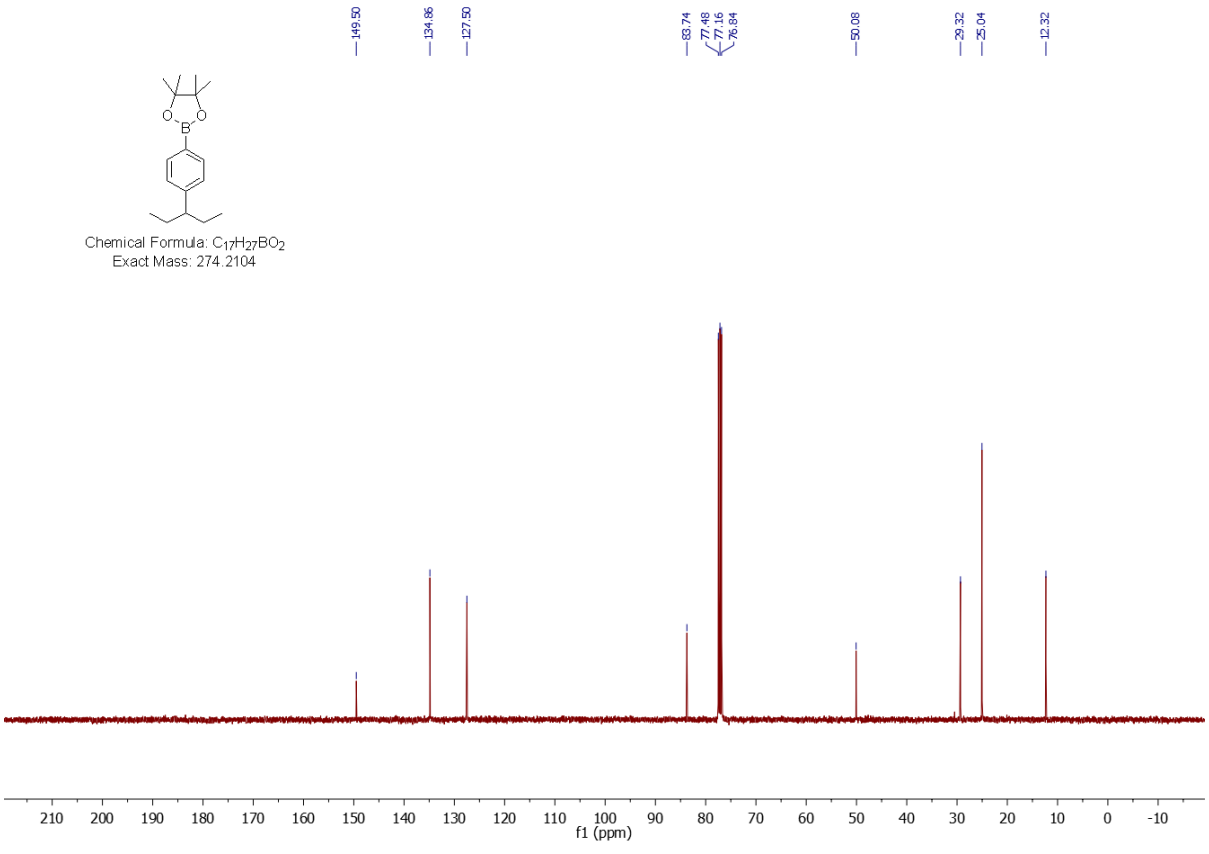

Cl
Chemical Formula: C11H15Cl
Exact Mass: 182.0862
7.25
7.23
7.06
7.04
7.03
2.32
2.31
2.30
2.29
2.28
2.27
2.25
2.25
2.23
2.22
1.71
1.70
1.69
1.69
1.67
1.66
1.65
1.64
1.63
1.62
1.56
1.55
1.54
1.53
1.52
1.51
1.50
1.49
1.48
1.46
1.46
0.77
0.75
0.73
0.00
1.97
1.96
1.00
2.25
2.38
6.12
f1 (ppm)

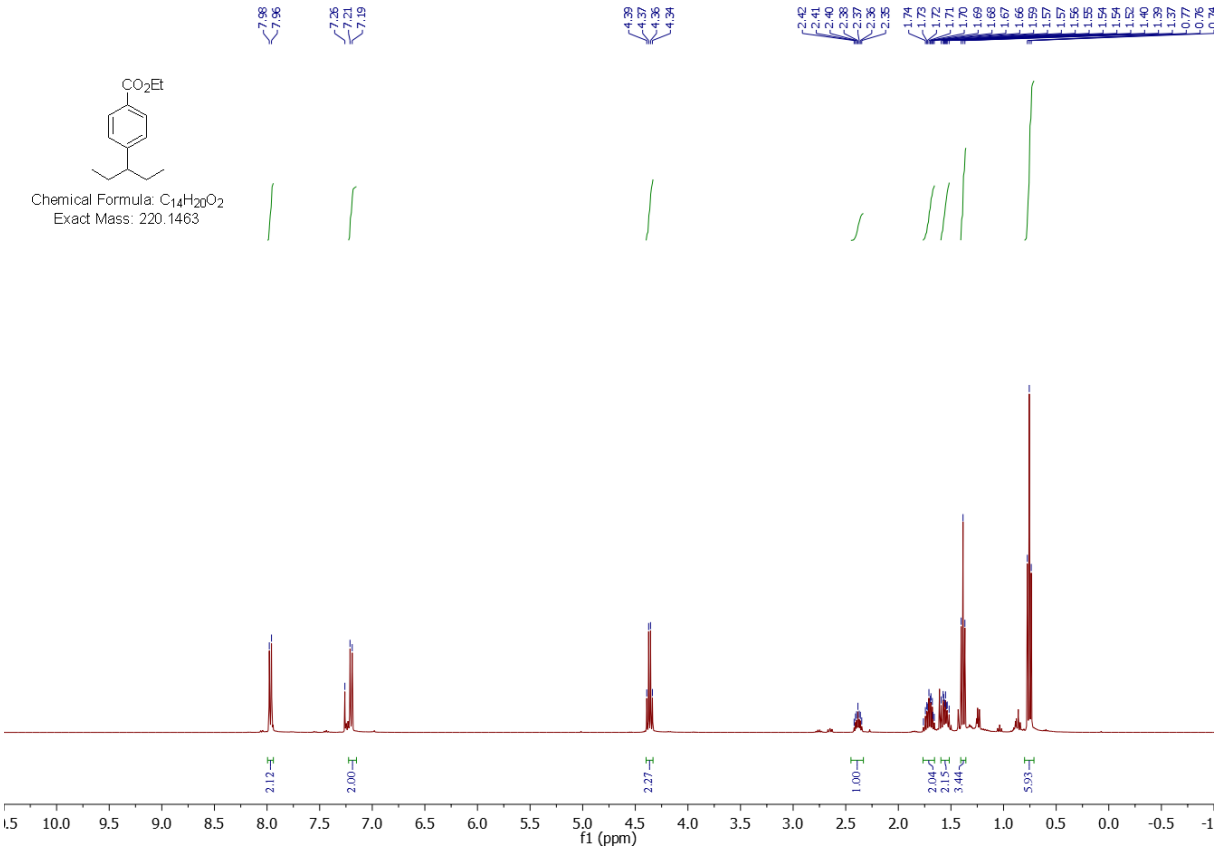

144.38
131.46
129.26
128.41
77.48
77.16
76.84
49.31
29.40
12.24
Cl
Chemical Formula: C11H15Cl
Exact Mass: 182.0862
f1 (ppm)

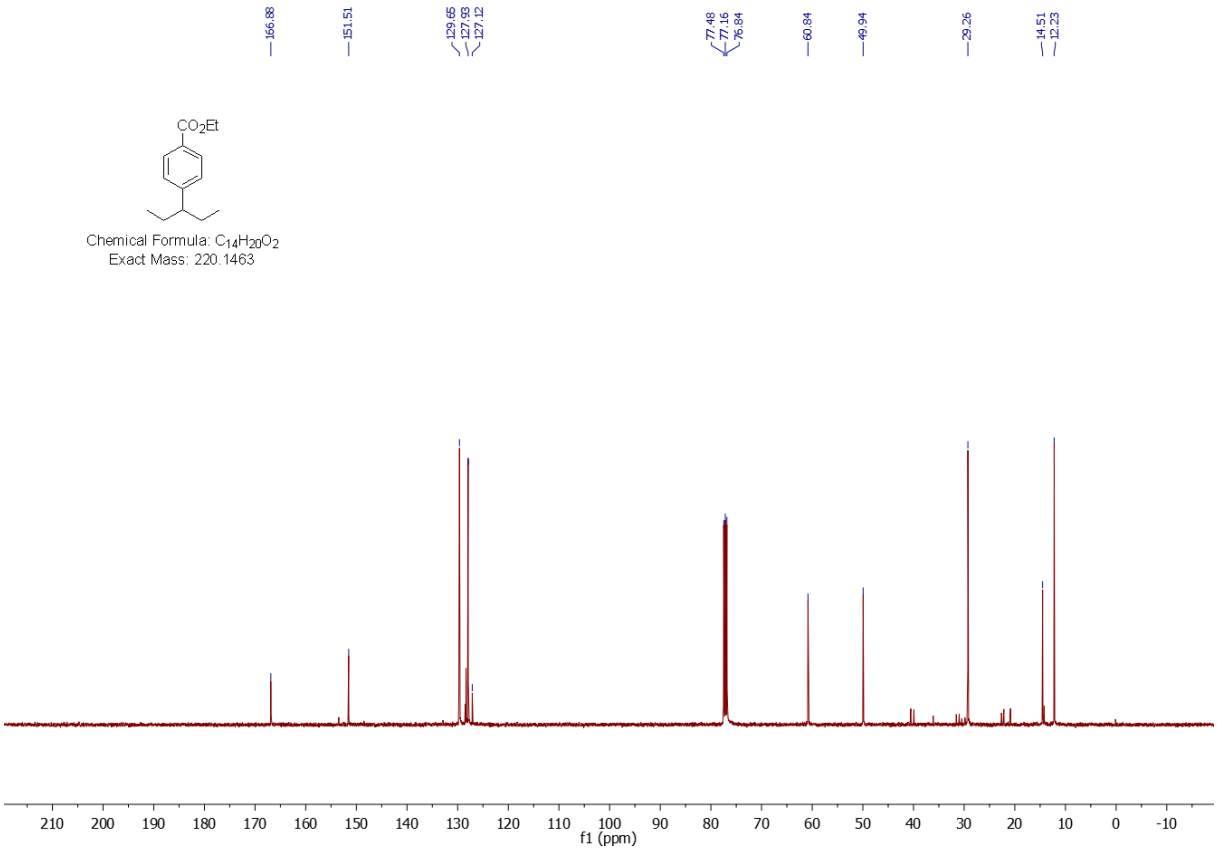

Ph
Chemical Formula: C17H20
Exact Mass: 224.1565
f1 (ppm)

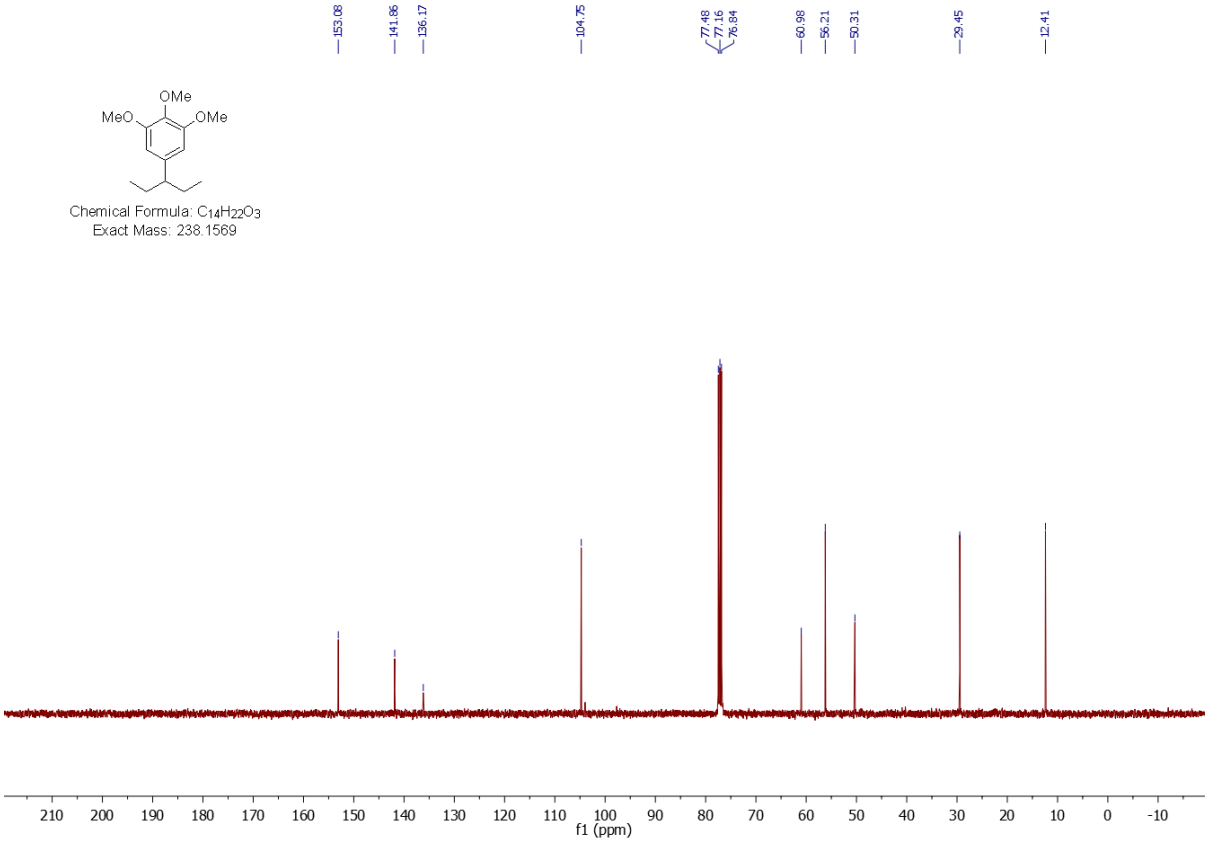

Ph
Chemical Formula: C17H20
Exact Mass: 224.1565
f1 (ppm)

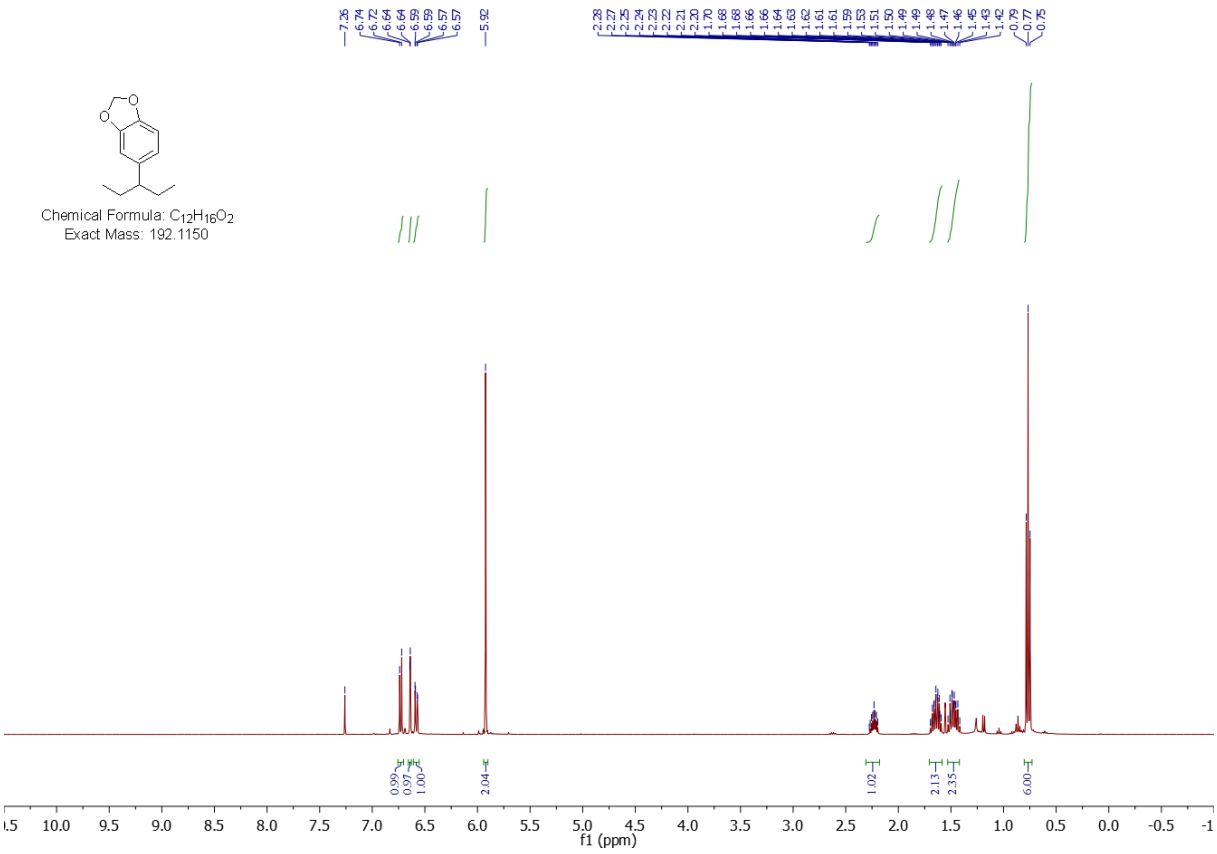

Chemical Formula: C17H27BO2
Exact Mass: 274.2104
f1 (ppm)

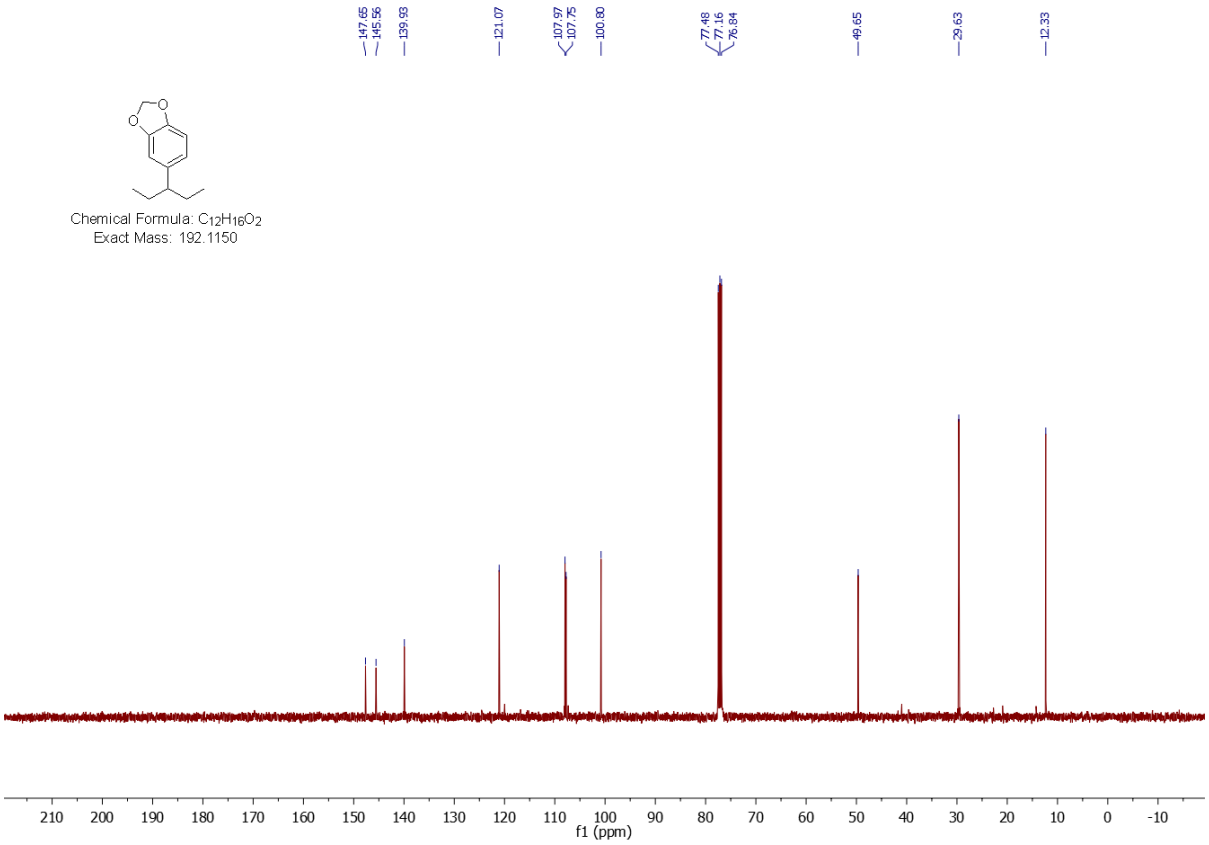

Chemical Formula: C17H27BO2
Exact Mass: 274.2104
f1 (ppm)

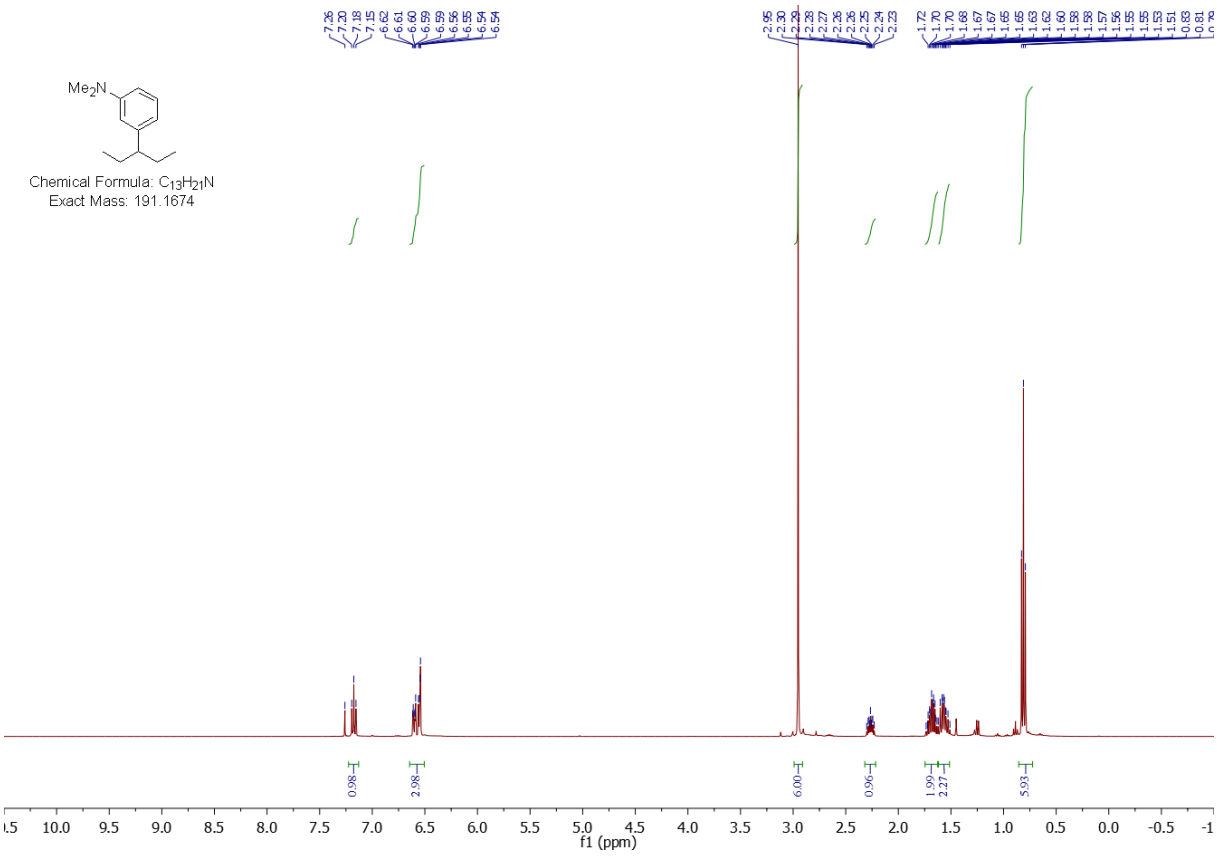

CO2Et
Chemical Formula: C14H20O2
Exact Mass: 220.1463
f1 (ppm)

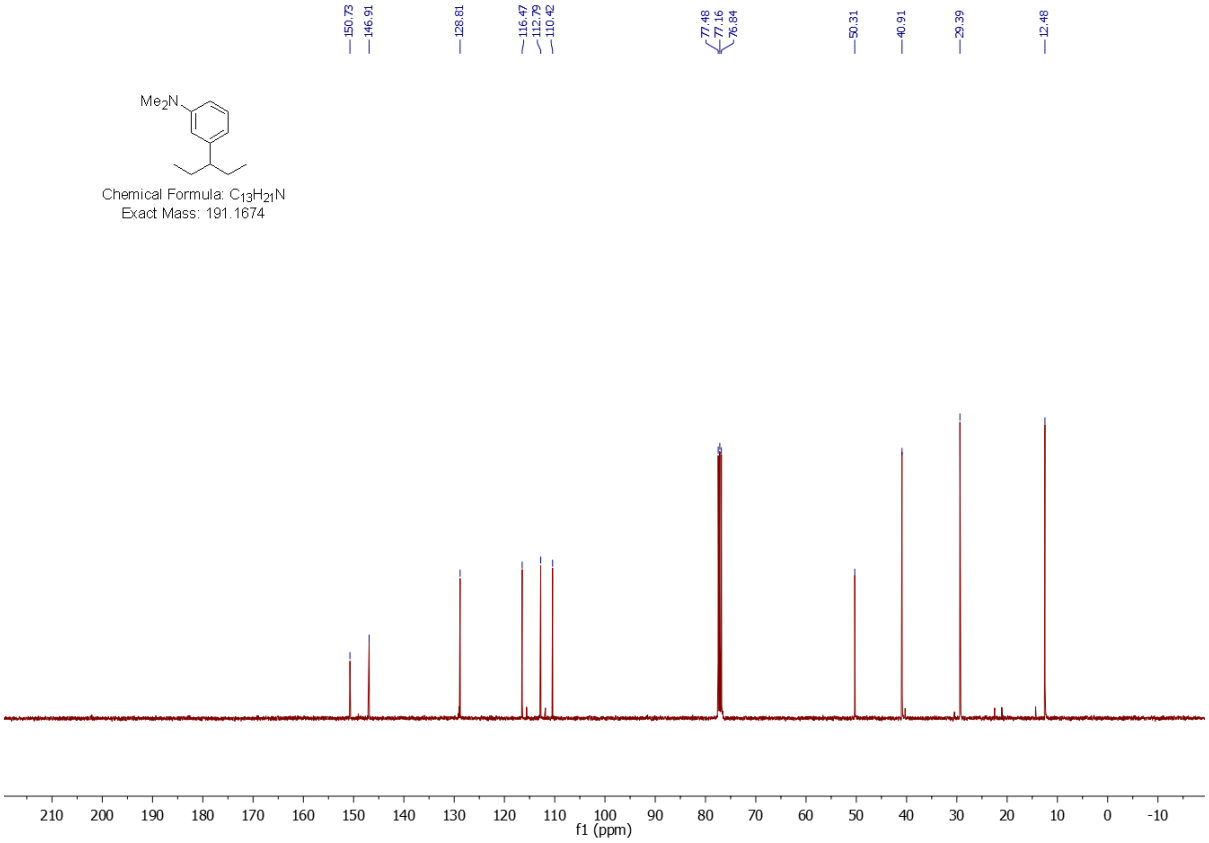

CO2Et
Chemical Formula: C14H20O2
Exact Mass: 220.1463
f1 (ppm)

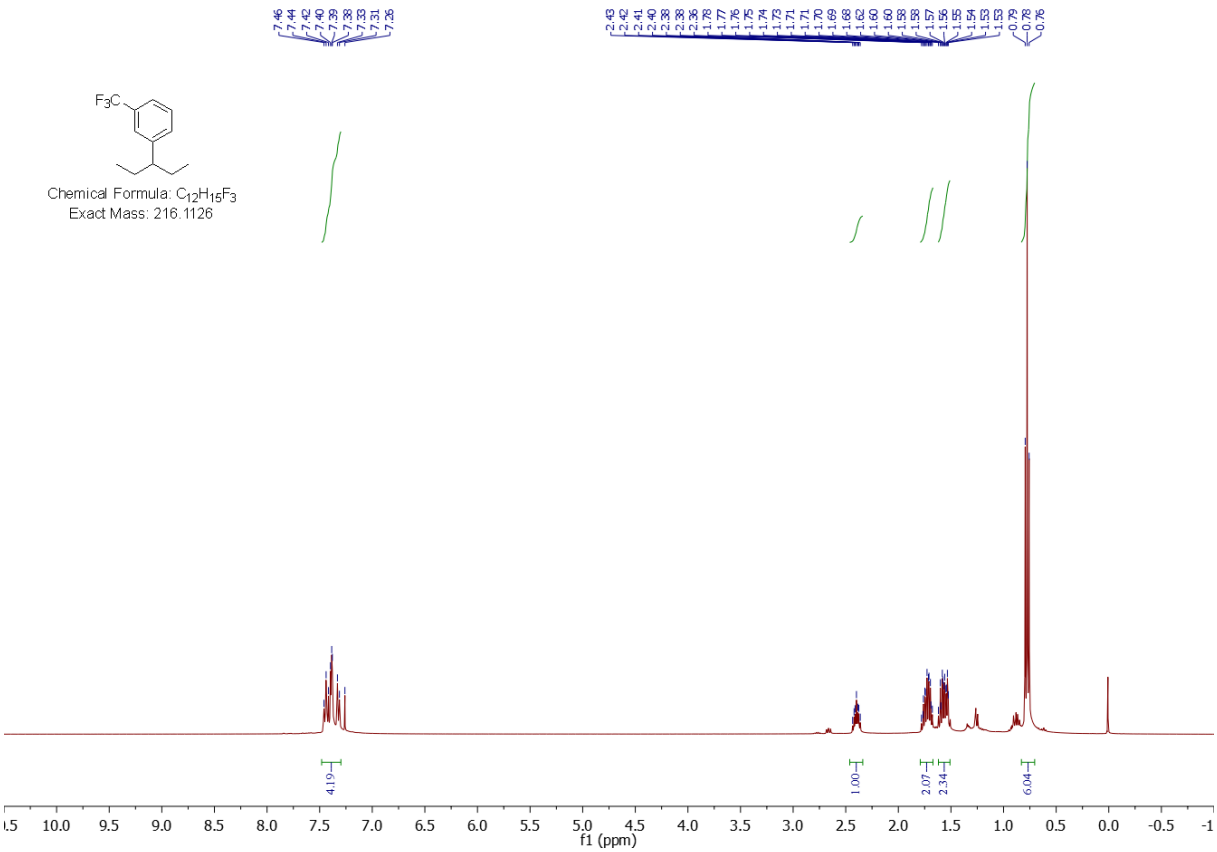

153.08
141.86
136.17
104.75
77.48
77.16
76.84
60.98
56.21
50.31
29.45
12.41
OMe
MeO
OMe
Chemical Formula: C14H22O3
Exact Mass: 238.1569
f1 (ppm)

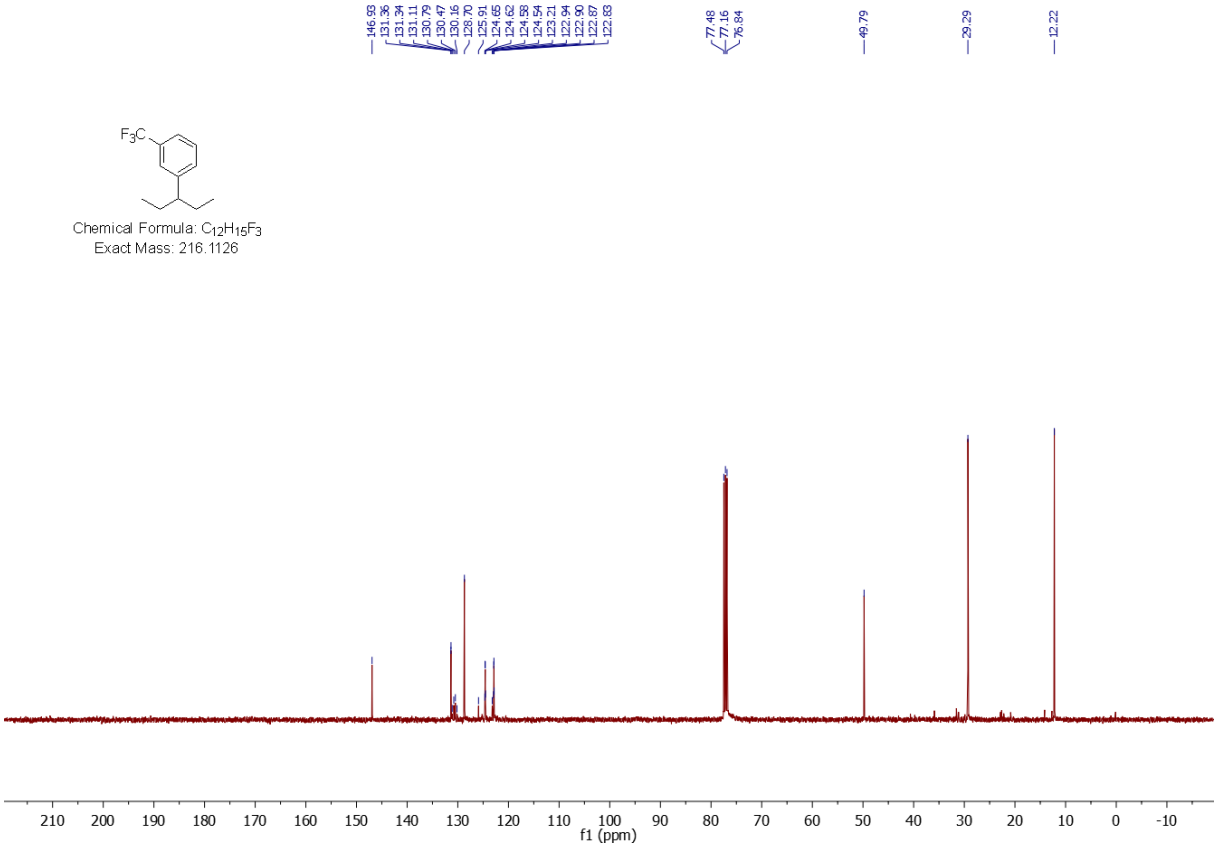

7.26
6.74
6.72
6.64
6.64
6.59
6.59
6.57
6.57
5.92
2.28
2.27
2.25
2.24
2.23
2.22
2.21
2.20
1.70
1.68
1.68
1.66
1.66
1.64
1.63
1.62
1.61
1.61
1.59
1.53
1.51
1.50
1.49
1.49
1.48
1.47
1.46
1.45
1.43
1.42
0.79
0.77
0.75
O
O
Chemical Formula: C12H16O2
Exact Mass: 192.1150
0.99
0.97
1.00
2.04
1.02
2.13
2.35
6.00
f1 (ppm)

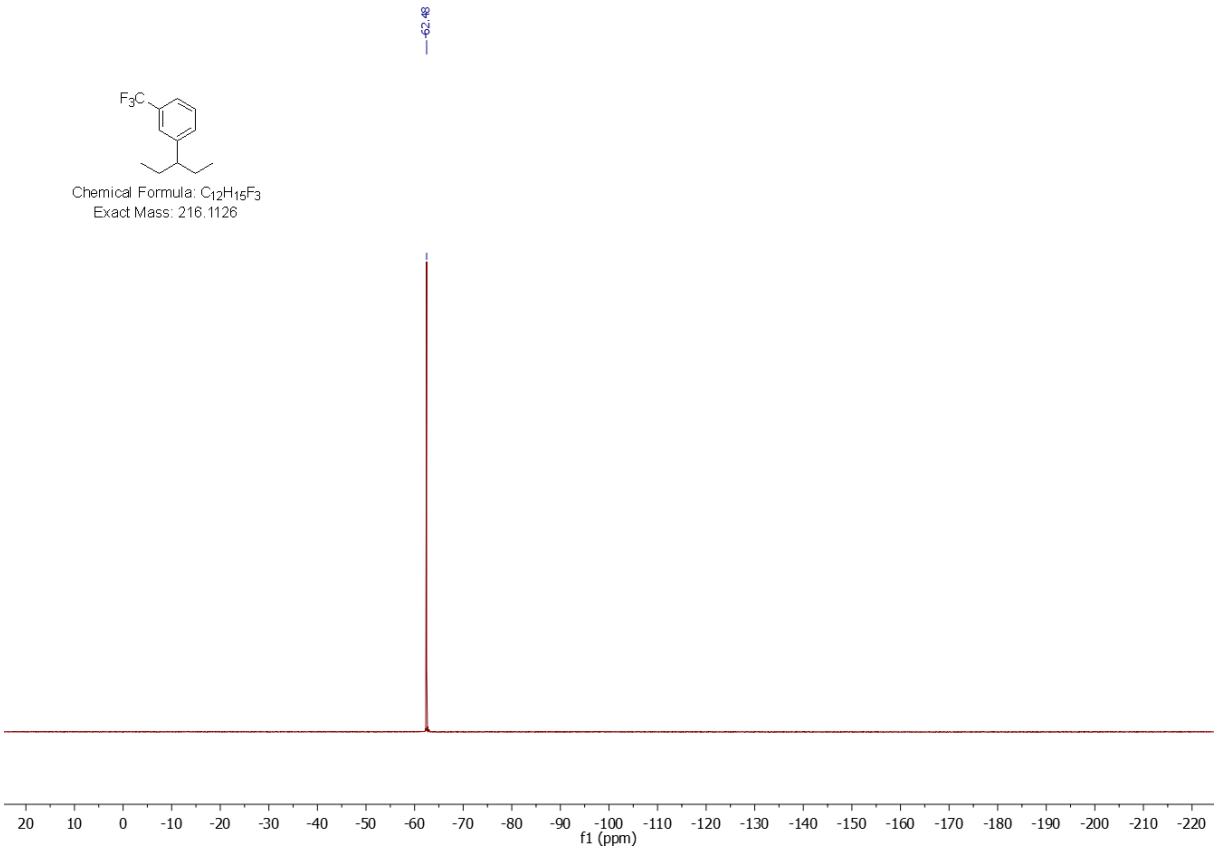

147.65
145.56
139.93
121.07
107.97
107.75
100.80
77.48
77.16
76.84
49.65
29.63
12.33
Chemical Formula: C12H16O2
Exact Mass: 192.1150
f1 (ppm)

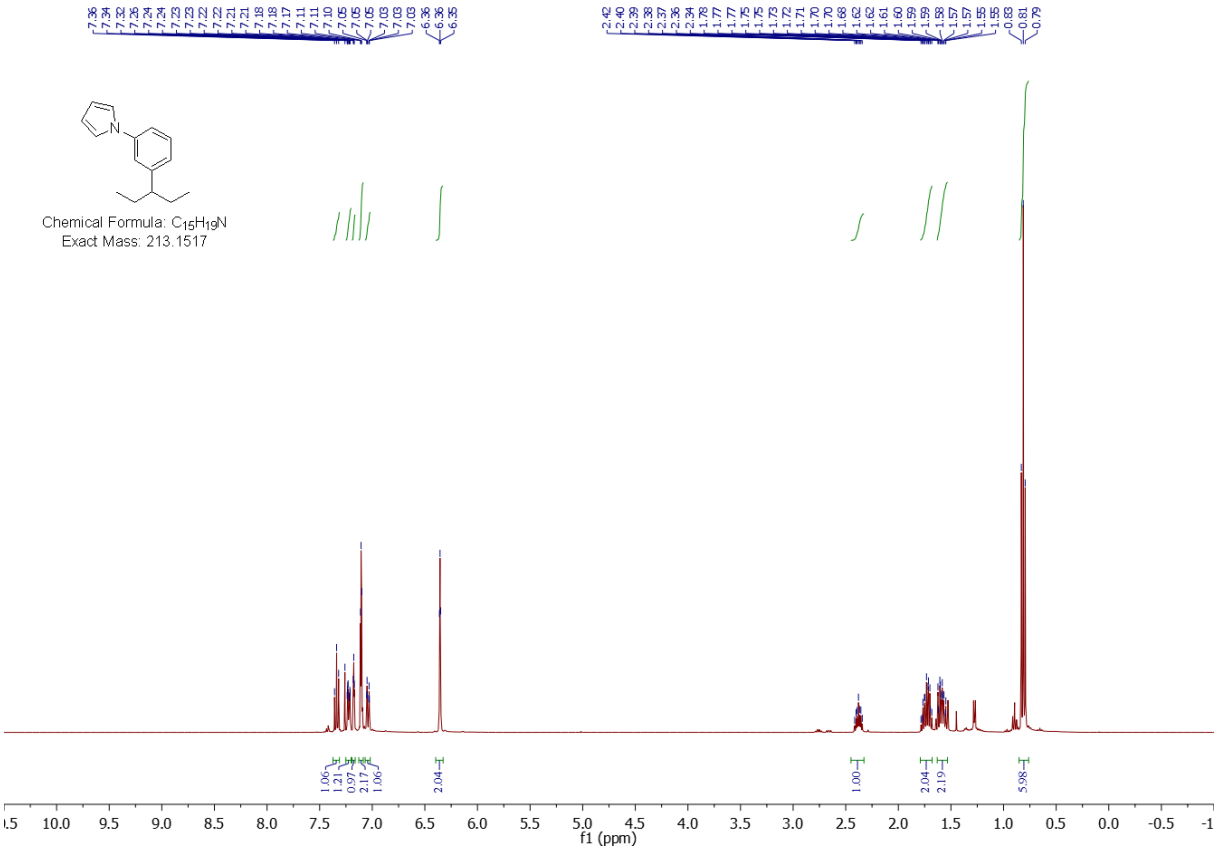

Me2N
Chemical Formula: C13H21N
Exact Mass: 191.1674
0.98
2.98
6.00
0.96
1.99
2.27
5.93
f1 (ppm)

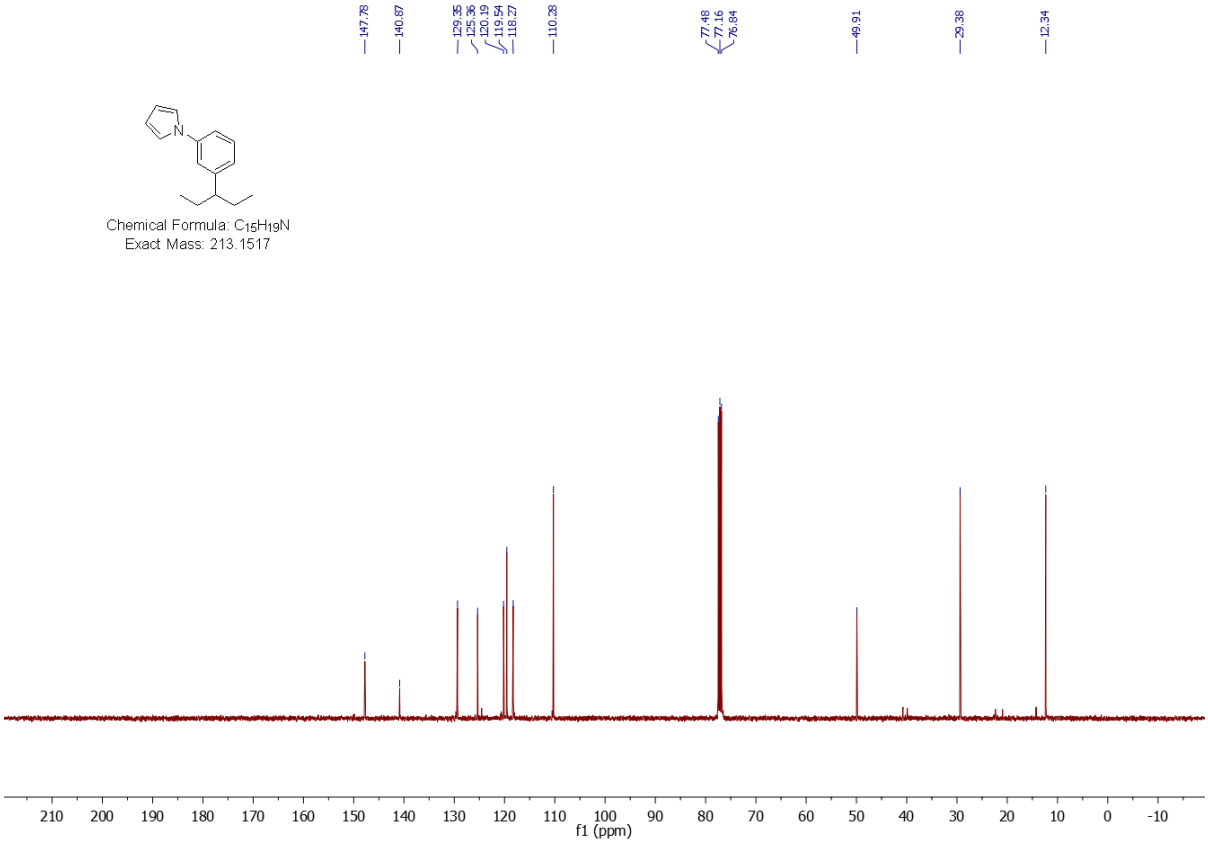

150.73
146.91
128.81
116.47
112.79
110.42
77.48
77.16
76.84
50.31
40.91
29.39
12.48
Me2N
Chemical Formula: C13H21N
Exact Mass: 191.1674
f1 (ppm)

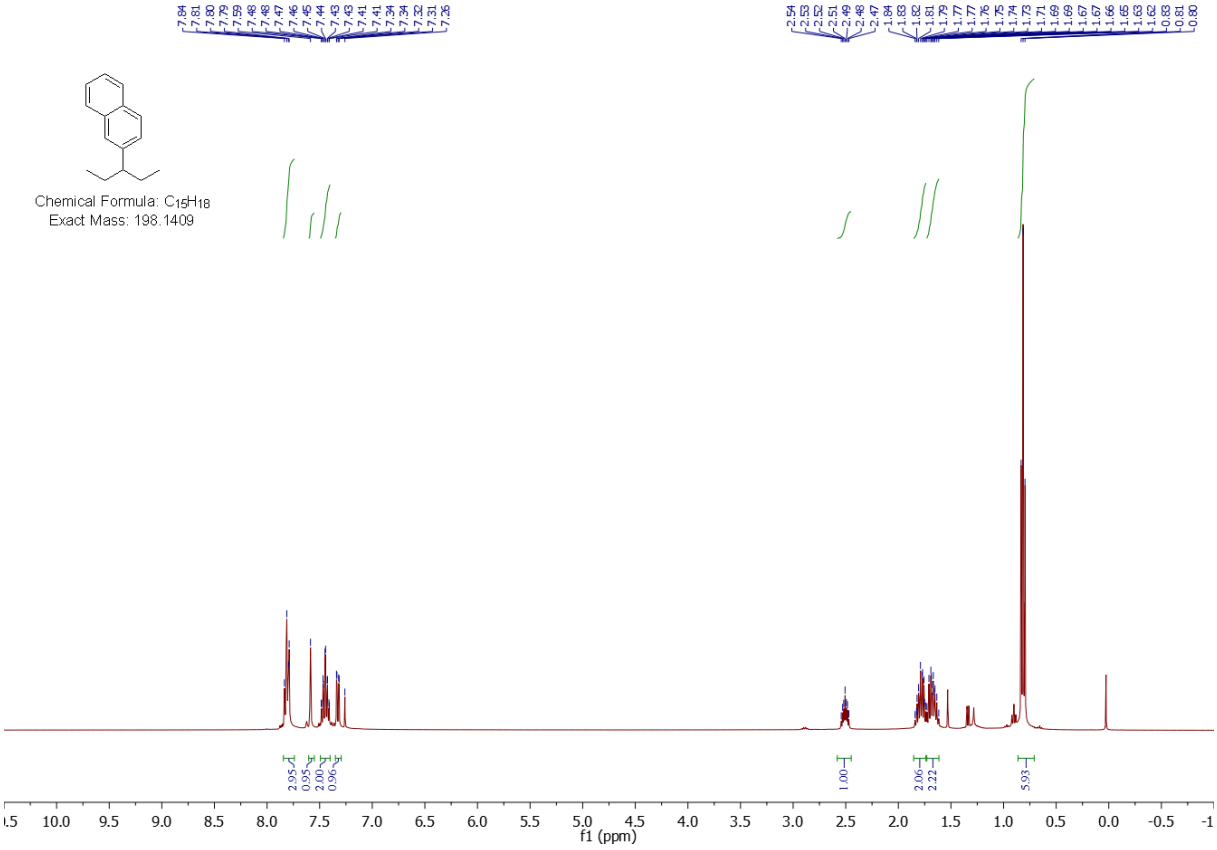

F3C
Chemical Formula: C12H15F3
Exact Mass: 216.1126
4.19
1.00
2.07
2.34
6.04
f1 (ppm)

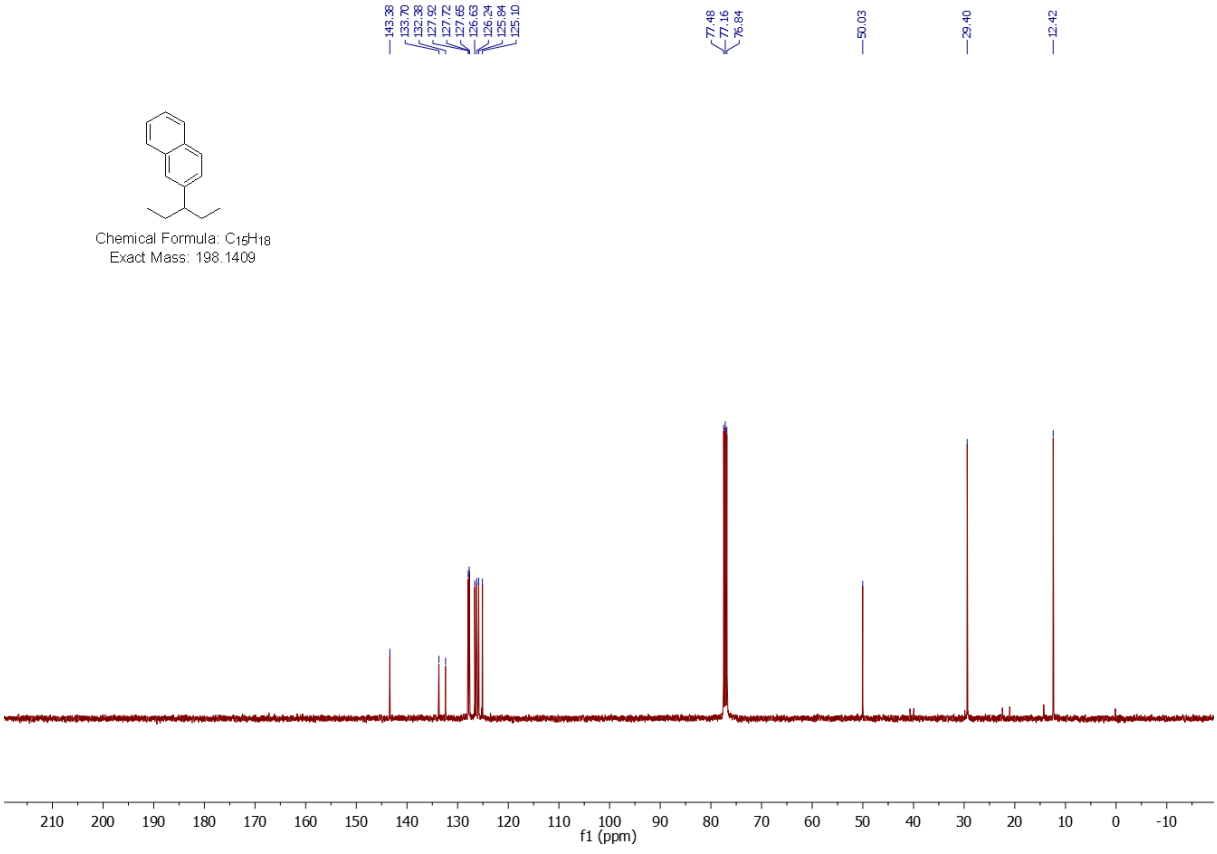

146.93
131.36
131.34
131.11
130.79
130.47
130.16
128.70
125.91
124.65
124.62
124.58
124.54
123.21
122.94
122.90
122.87
122.83
77.48
77.16
76.84
49.79
29.29
12.22
F3C
Chemical Formula: C12H15F3
Exact Mass: 216.1126
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

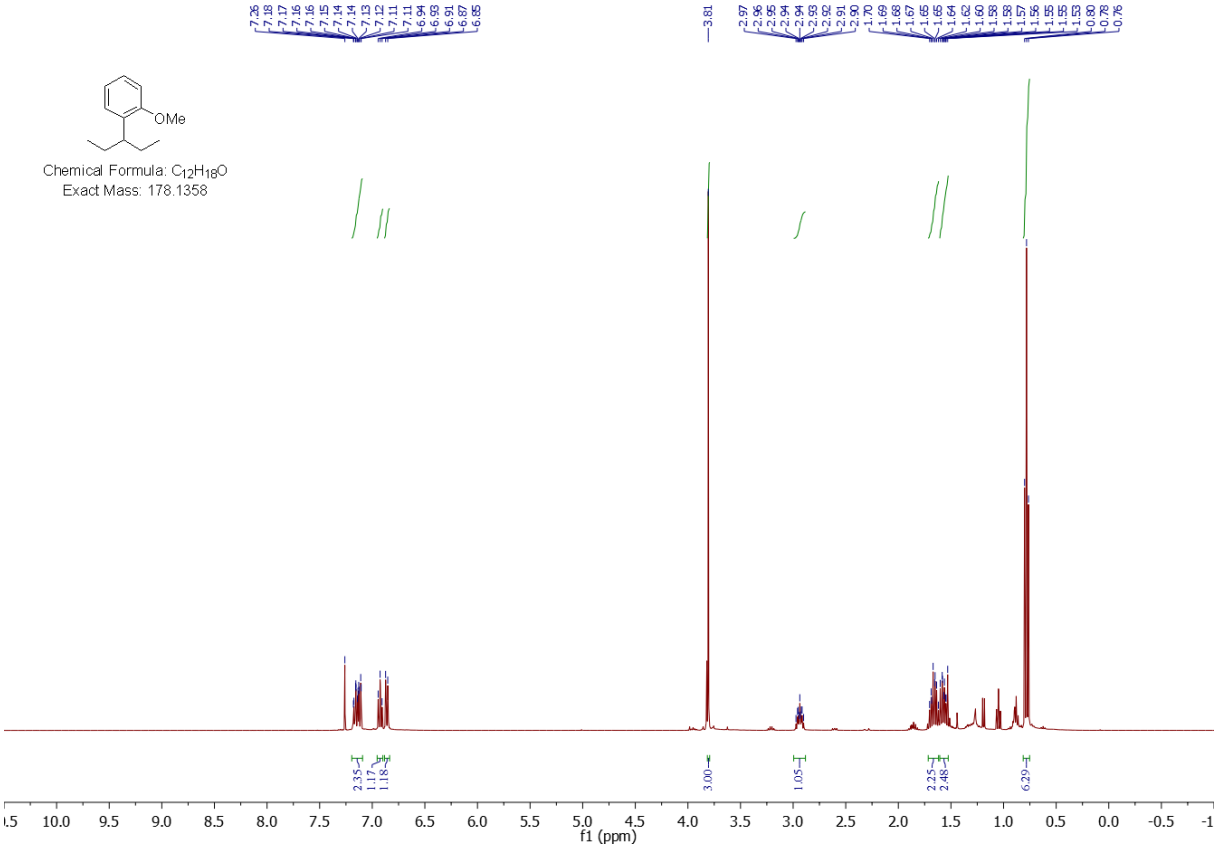

-62.48
F3C
Chemical Formula: C12H15F3
Exact Mass: 216.1126
20 10 0 -10 -20 -30 -40 -50 -60 -70 -80 -90 -100 -110 -120 -130 -140 -150 -160 -170 -180 -190 -200 -210 -220
f1 (ppm)

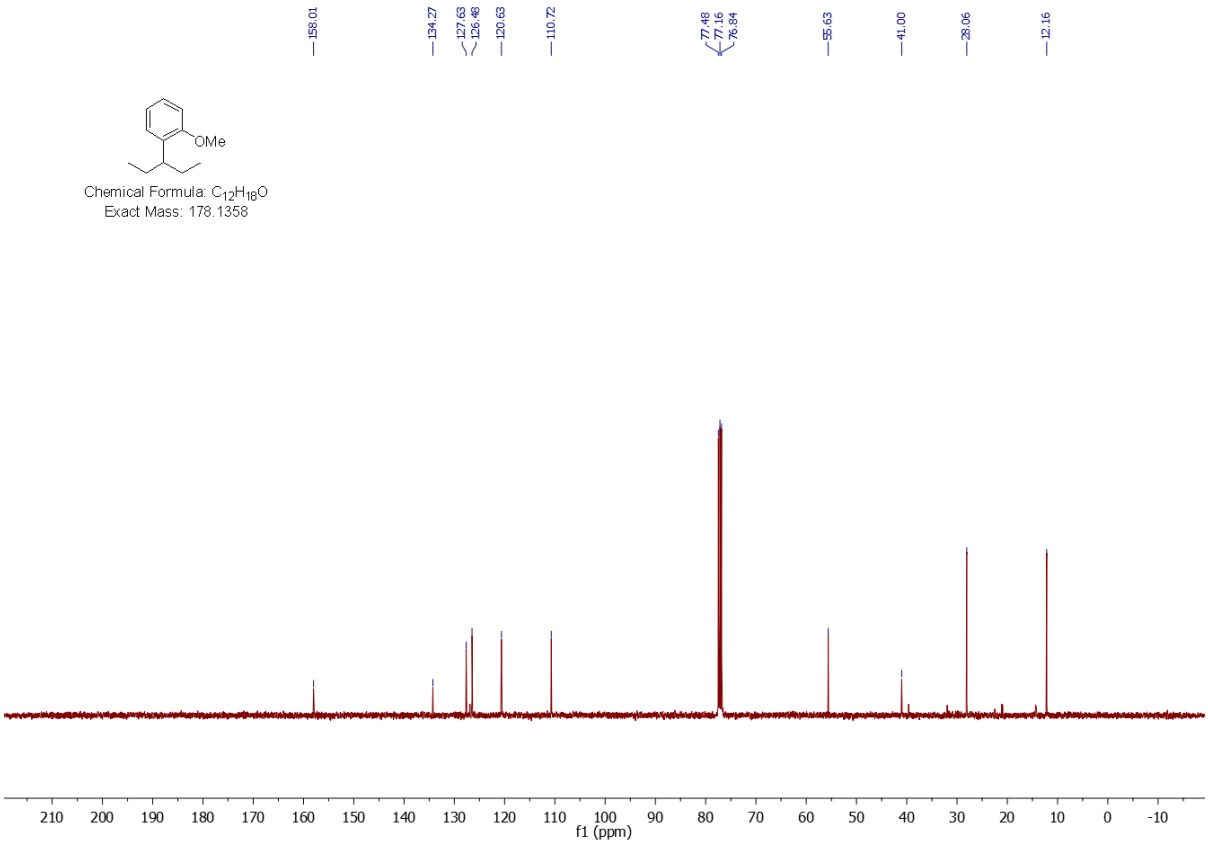

Chemical Formula: C15H19N
Exact Mass: 213.1517
f1 (ppm)

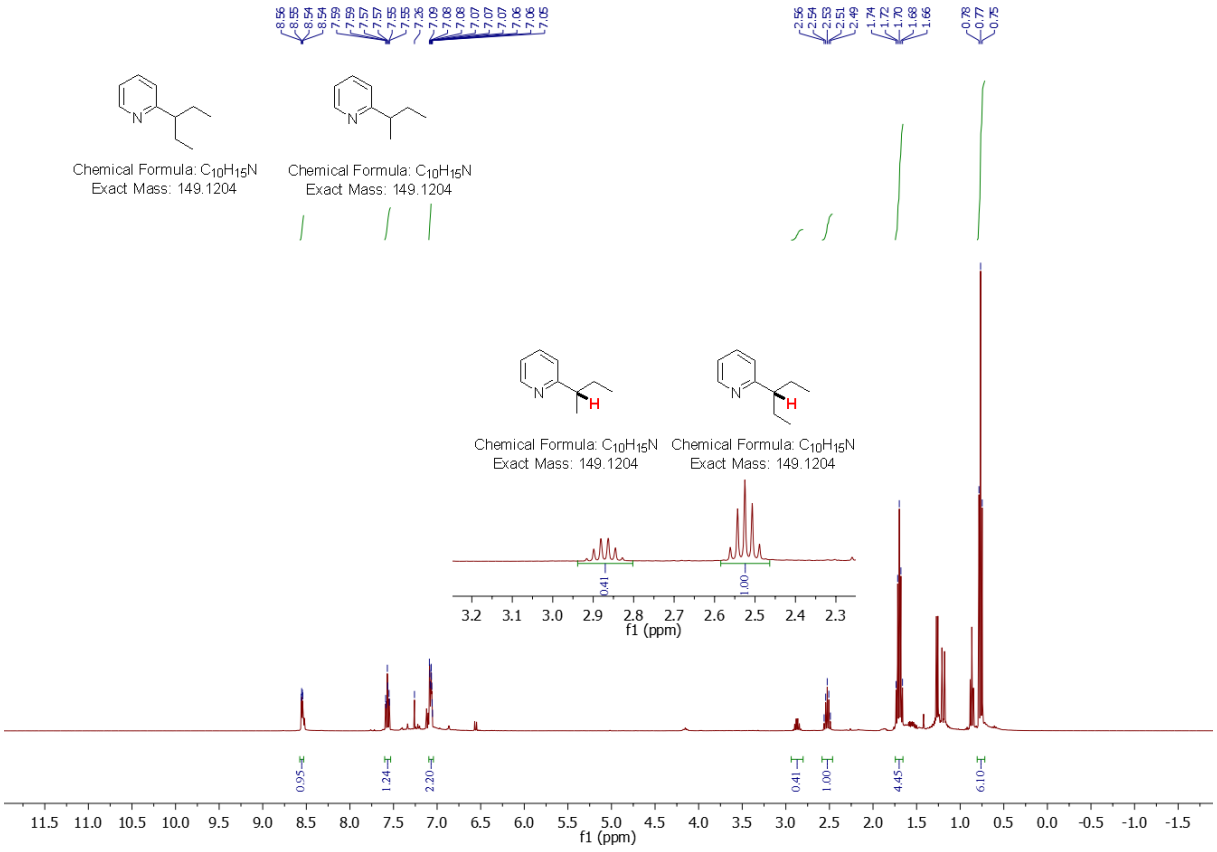

Chemical Formula: C15H19N
Exact Mass: 213.1517
f1 (ppm)

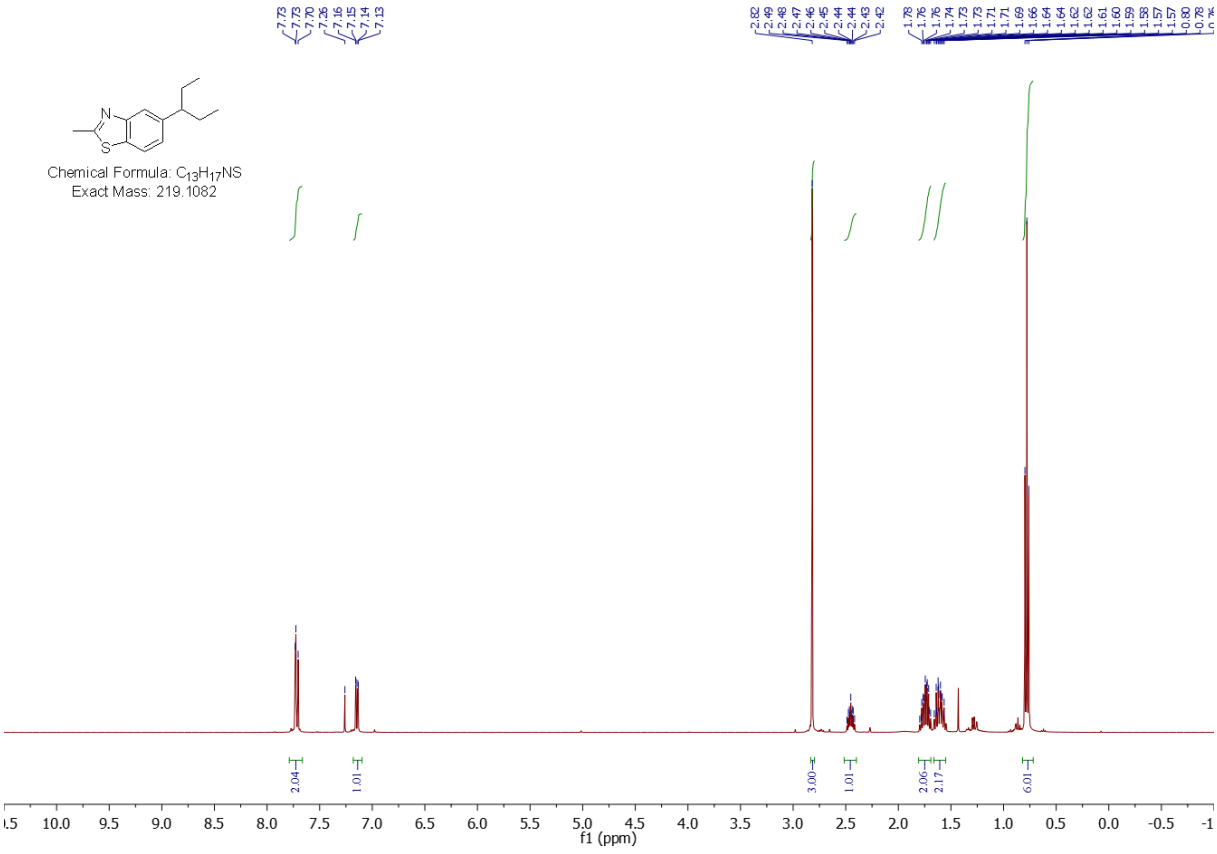

Chemical Formula: C15H18
Exact Mass: 198.1409
f1 (ppm)

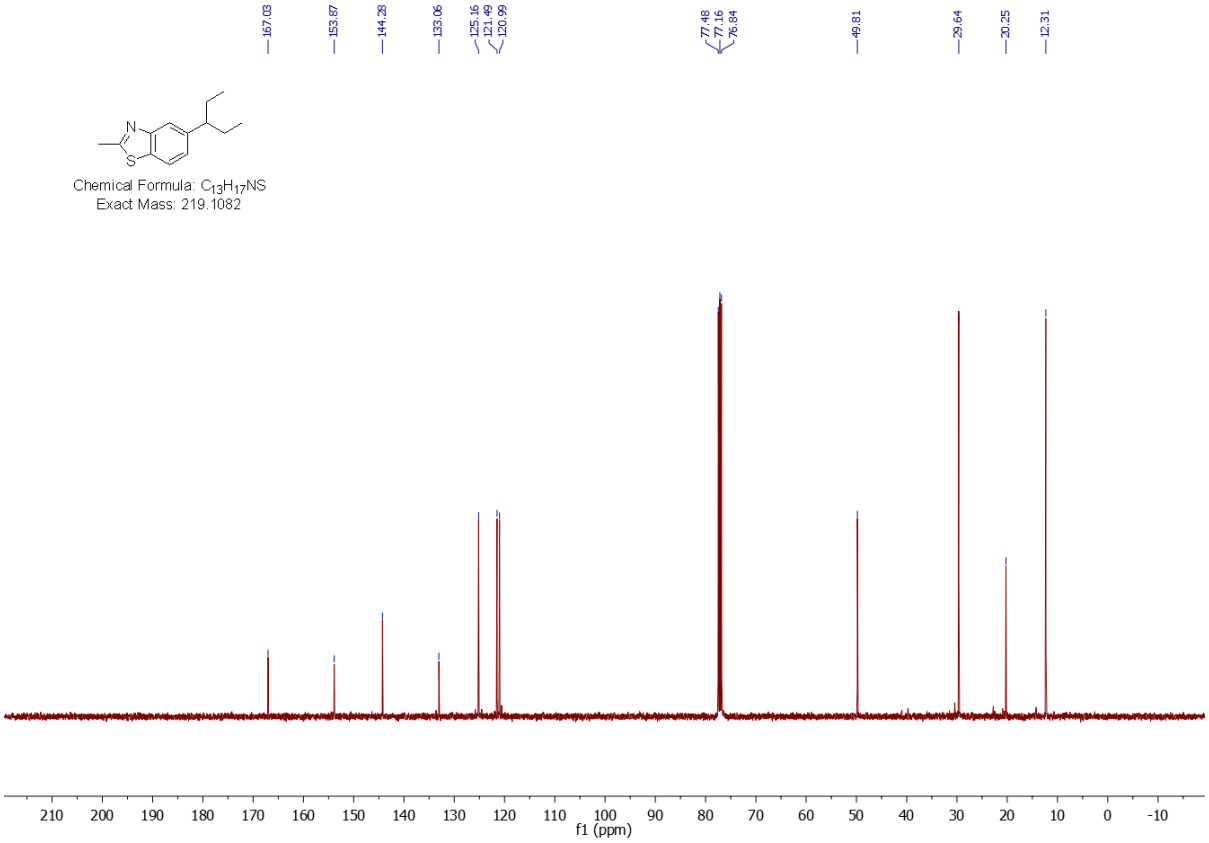

Chemical Formula: C15H18
Exact Mass: 198.1409
f1 (ppm)

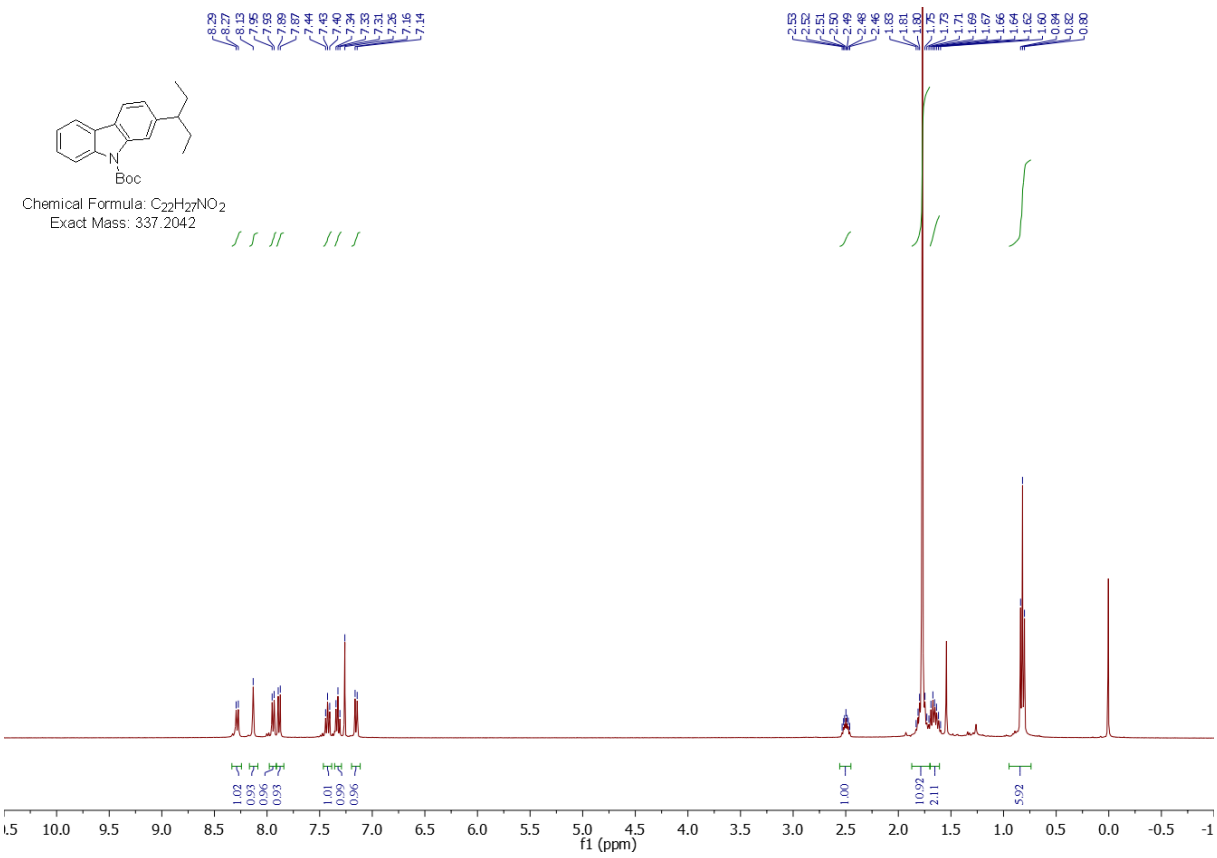

OMe
Chemical Formula: C12H18O
Exact Mass: 178.1358
f1 (ppm)

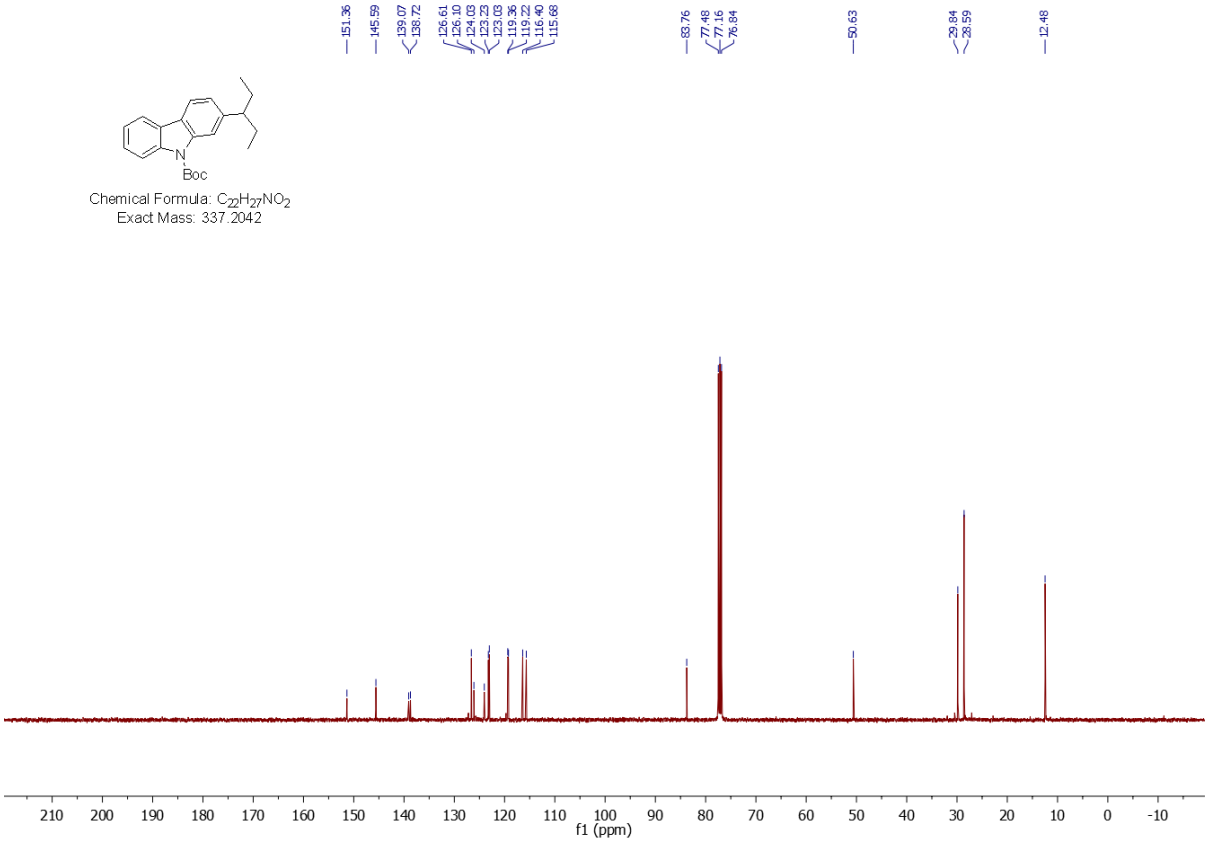

OMe
Chemical Formula: C12H18O
Exact Mass: 178.1358
f1 (ppm)

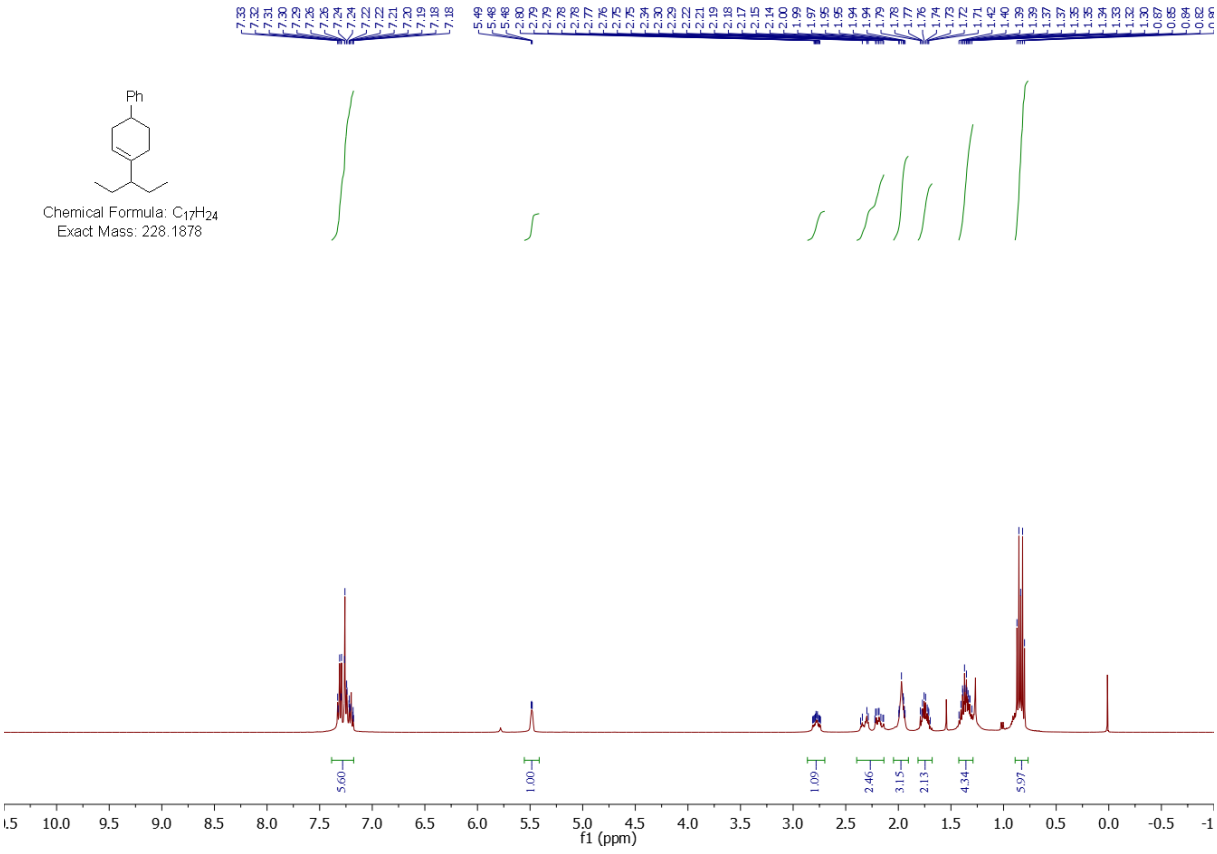

Chemical Formula: C10H15N
Exact Mass: 149.1204
Chemical Formula: C10H15N
Exact Mass: 149.1204
Chemical Formula: C10H15N
Exact Mass: 149.1204
Chemical Formula: C10H15N
Exact Mass: 149.1204
f1 (ppm)

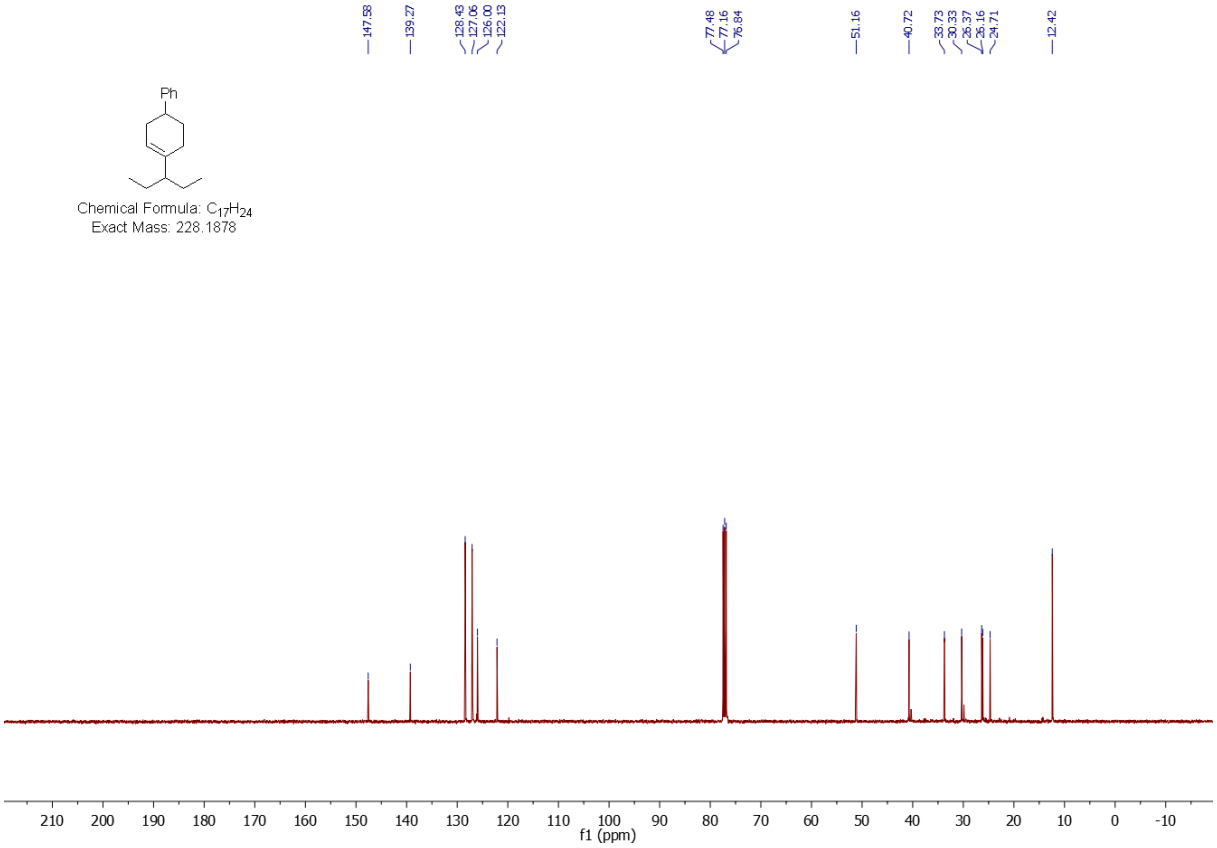

Chemical Formula: C13H17NS
Exact Mass: 219.1082
f1 (ppm)

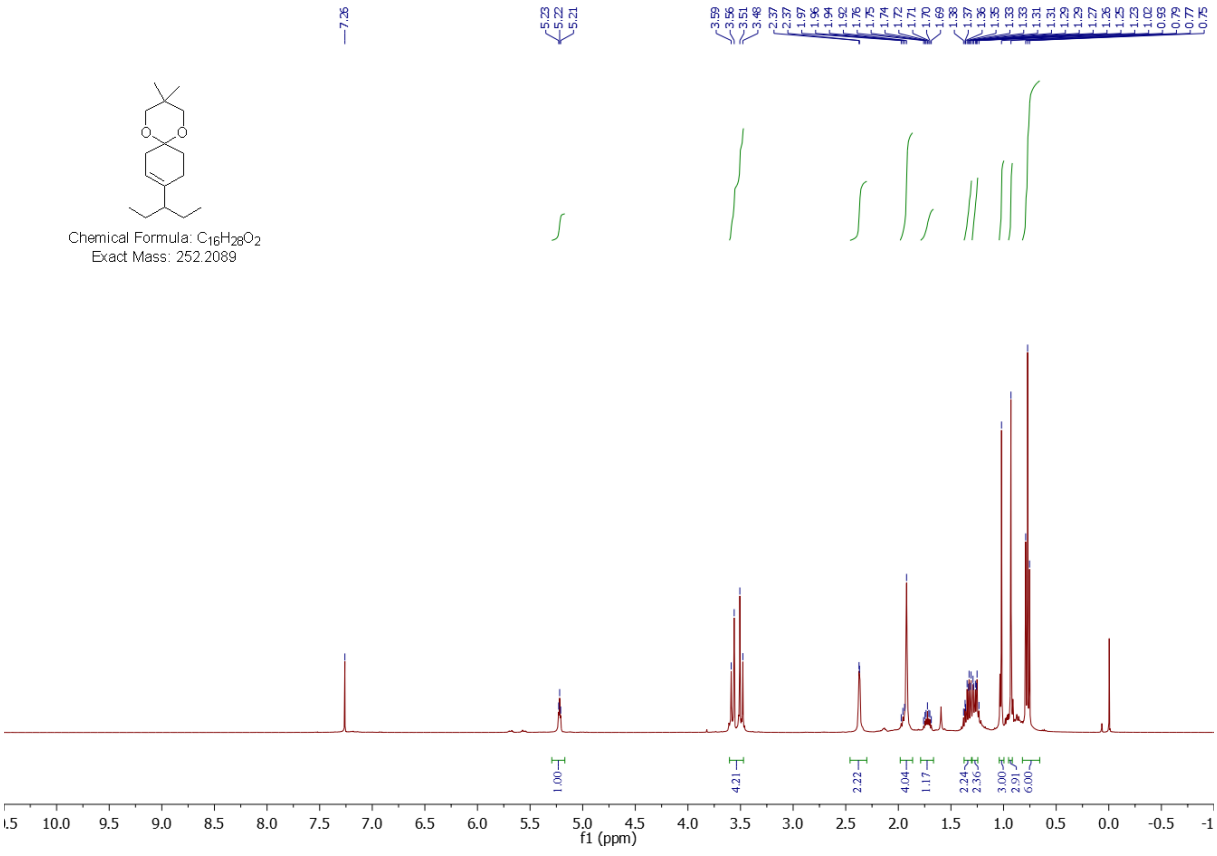

167.03
153.87
144.28
133.06
125.16
121.49
120.99
77.48
77.16
76.84
49.81
29.64
20.25
12.31
N
S
Chemical Formula: C13H17NS
Exact Mass: 219.1082
f1 (ppm)

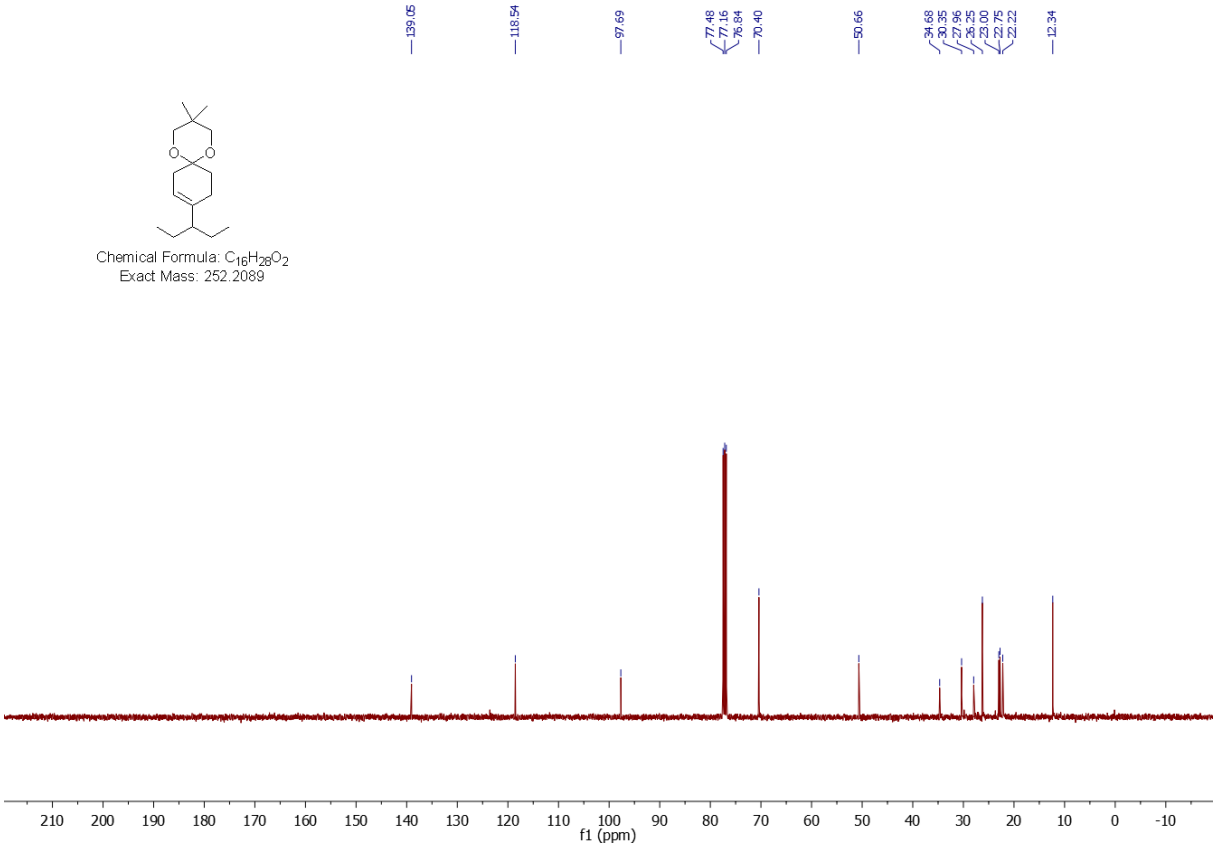

8.29
8.27
8.13
7.95
7.93
7.89
7.87
7.44
7.43
7.40
7.34
7.33
7.31
7.26
7.16
7.14
2.53
2.52
2.51
2.50
2.49
2.48
2.46
1.83
1.81
1.80
1.75
1.73
1.71
1.69
1.67
1.66
1.64
1.62
1.60
0.84
0.82
0.80
N
Boc
Chemical Formula: C22H27NO2
Exact Mass: 337.2042
1.02
0.93
0.96
0.93
1.01
0.99
0.96
1.00
10.92
2.11
5.92
f1 (ppm)

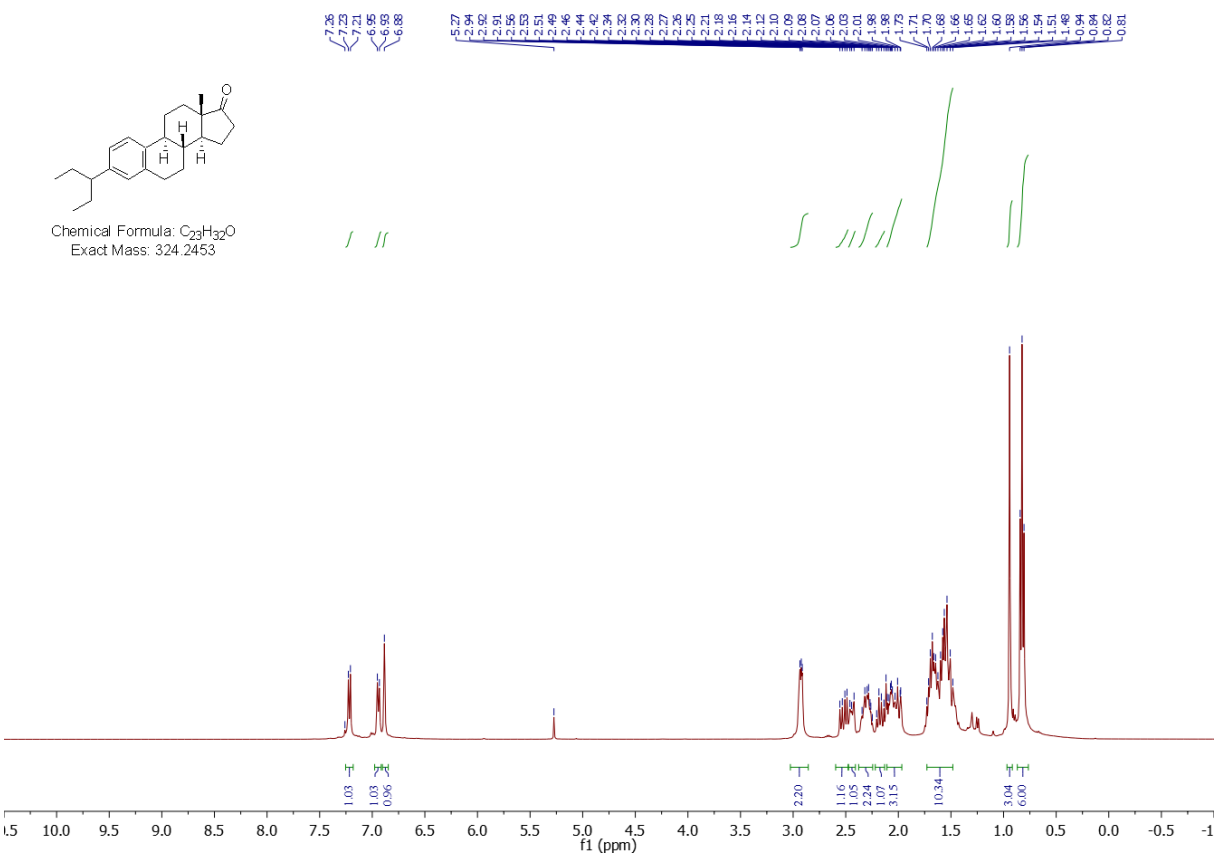

151.36
145.59
139.07
138.72
126.61
126.10
124.03
123.23
123.03
119.36
119.22
116.40
115.68
83.76
77.48
77.16
76.84
50.63
29.84
28.59
12.48
N
Boc
Chemical Formula: C22H27NO2
Exact Mass: 337.2042
f1 (ppm)

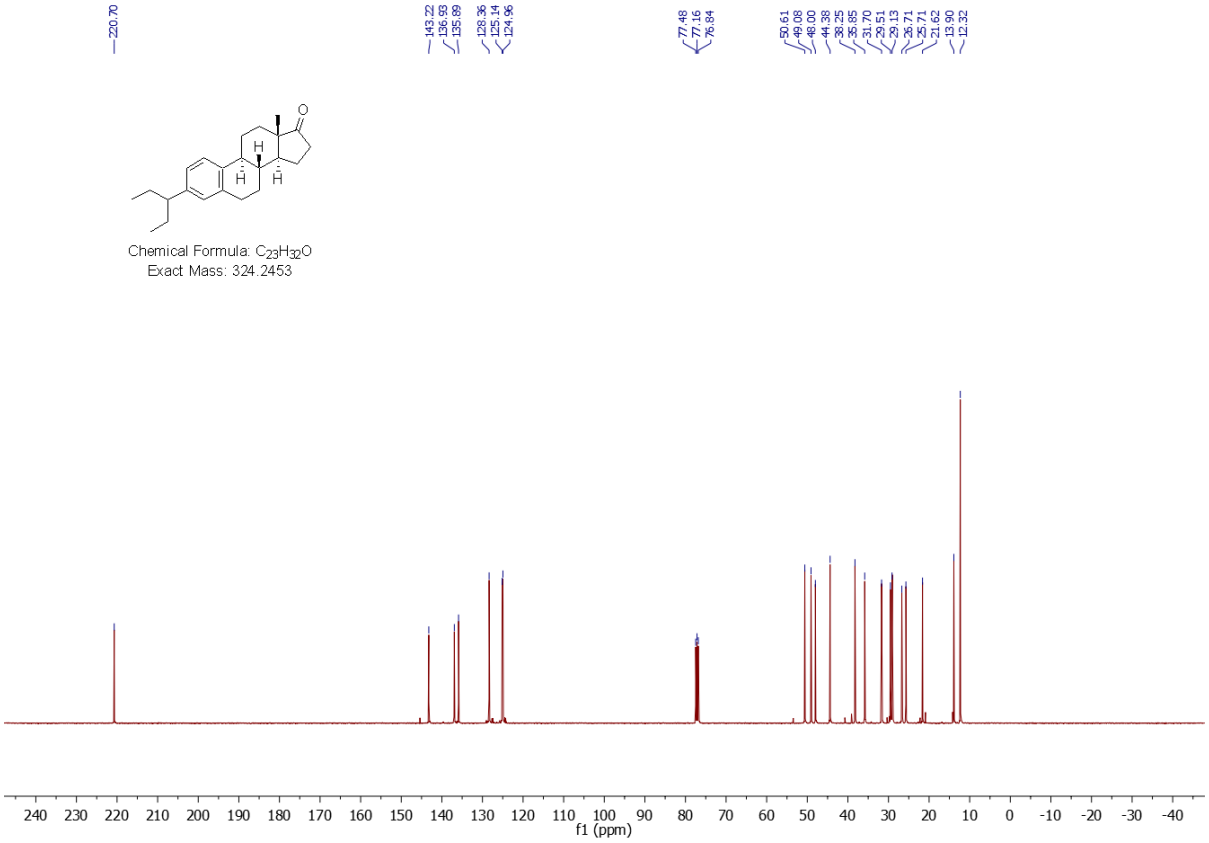

Ph
Chemical Formula: C17H24
Exact Mass: 228.1878
5.60
1.00
1.09
2.46
3.15
2.13
4.34
5.97
f1 (ppm)

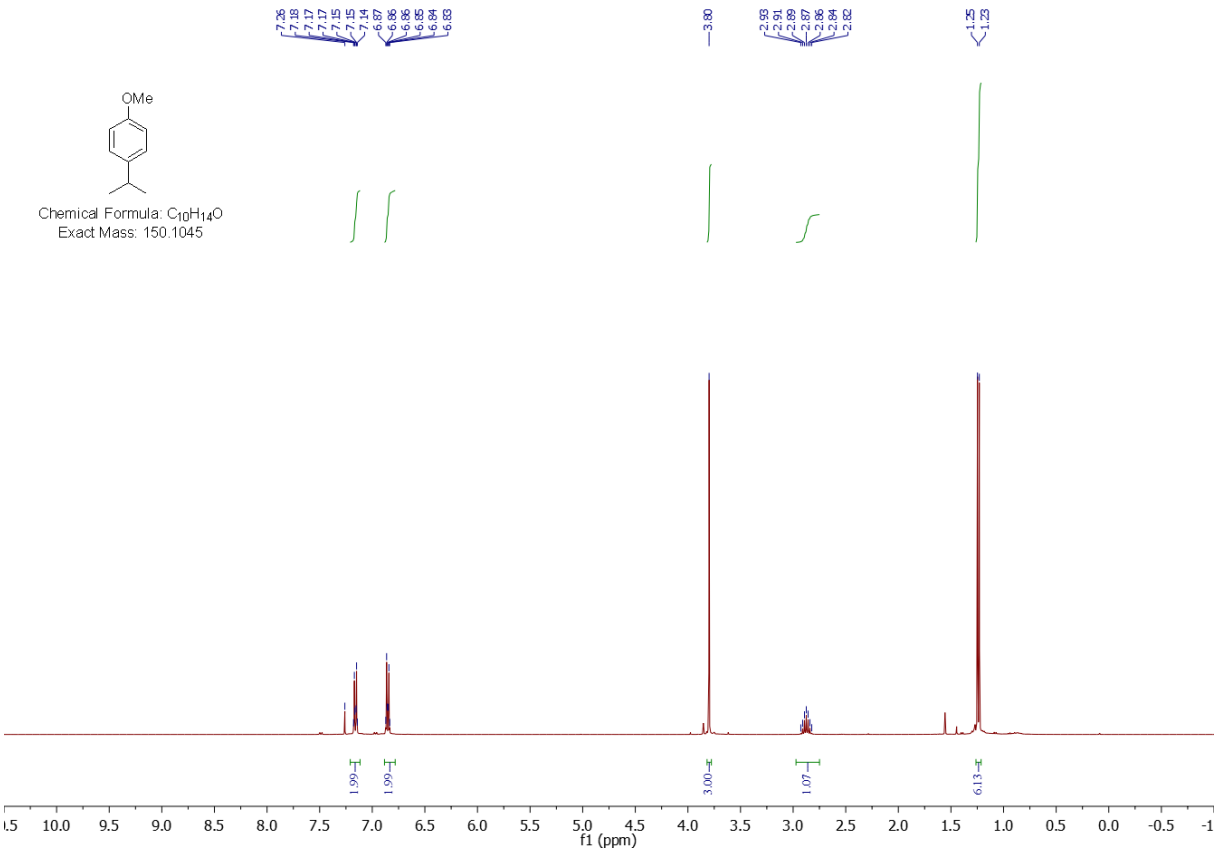

147.58
139.27
128.43
127.06
126.00
122.13
77.48
77.16
76.84
51.16
40.72
33.73
30.33
26.37
25.16
24.71
12.42
Ph
Chemical Formula: C17H24
Exact Mass: 228.1878
f1 (ppm)

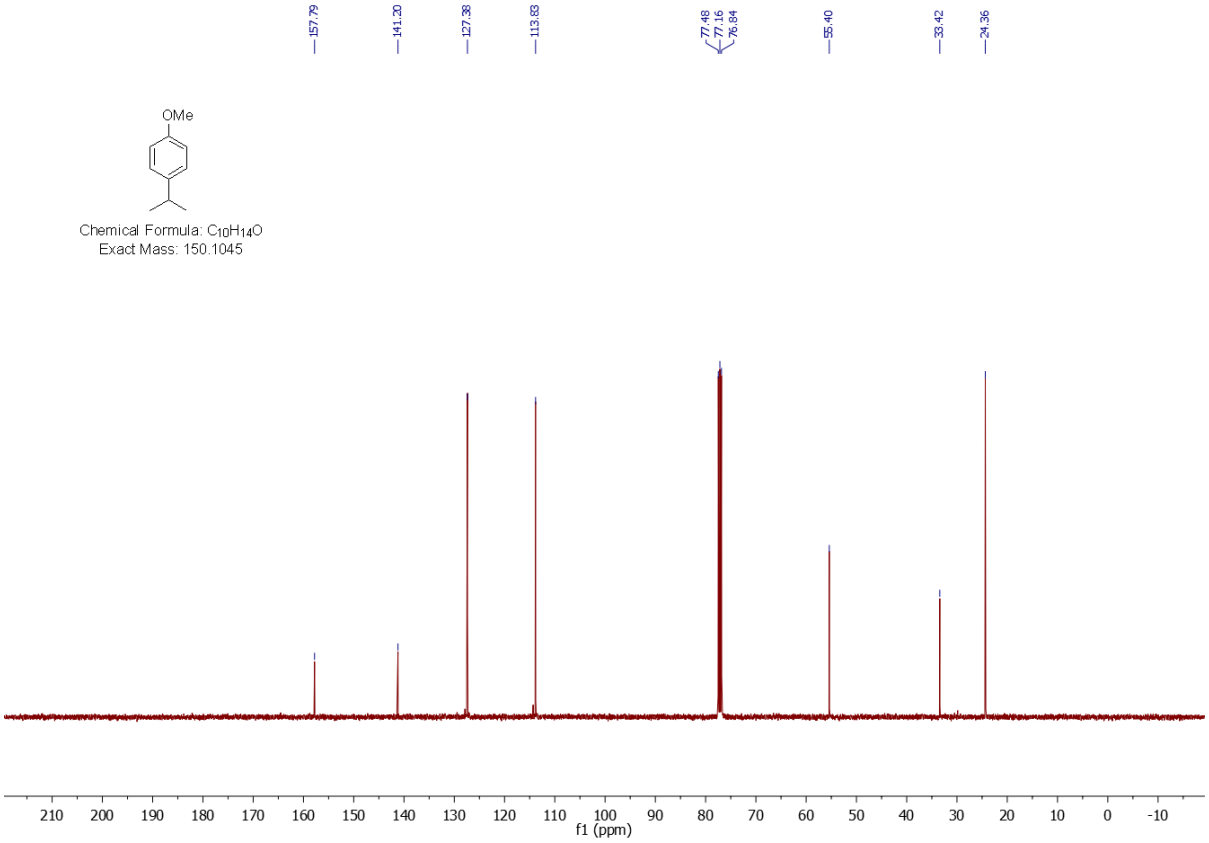

7.26
5.23
5.22
5.21
3.59
3.56
3.51
3.48
2.37
2.37
1.97
1.96
1.94
1.92
1.76
1.75
1.74
1.72
1.71
1.70
1.69
1.38
1.37
1.36
1.35
1.33
1.33
1.31
1.31
1.29
1.29
1.27
1.26
1.25
1.23
1.02
0.93
0.79
0.77
0.75
Chemical Formula: C16H28O2
Exact Mass: 252.2089
1.00
4.21
2.22
4.04
1.17
2.24
2.36
3.00
2.91
6.00
f1 (ppm)

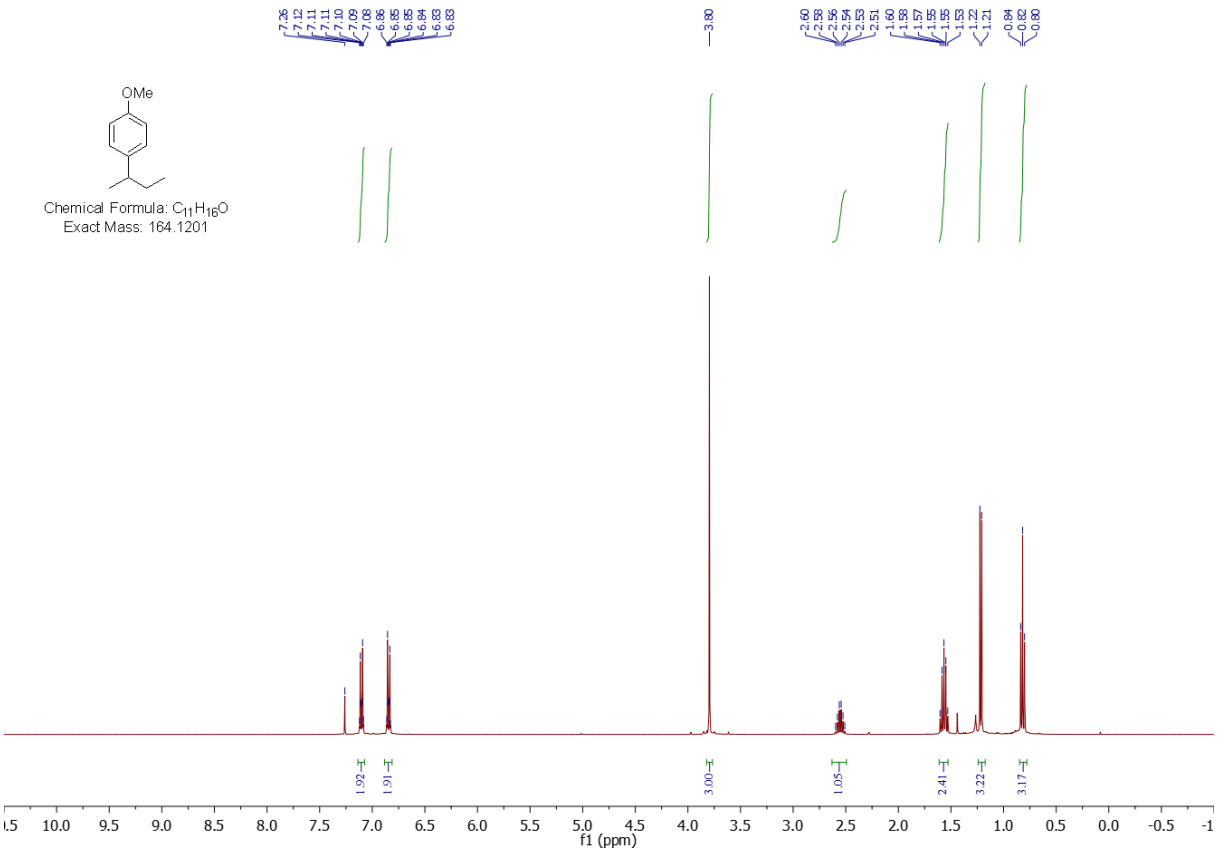

139.05
118.54
97.69
77.48
77.16
76.84
70.40
50.66
34.68
30.35
27.96
26.25
23.00
22.75
22.22
12.34
Chemical Formula: C16H28O2
Exact Mass: 252.2089
f1 (ppm)

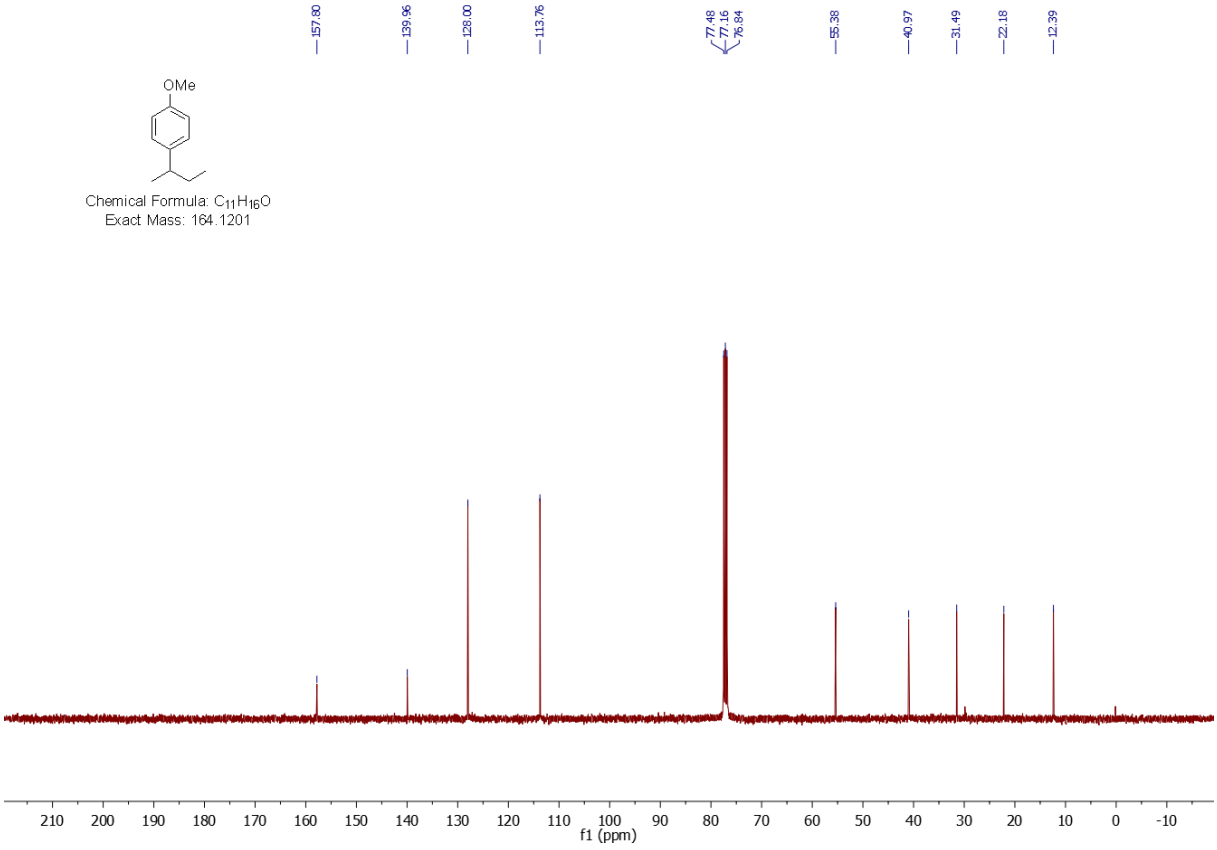

Chemical Formula: C23H32O
Exact Mass: 324.2453
1.03
1.03
0.96
2.20
1.16
1.05
2.24
1.07
3.15
10.34
3.04
6.00
f1 (ppm)

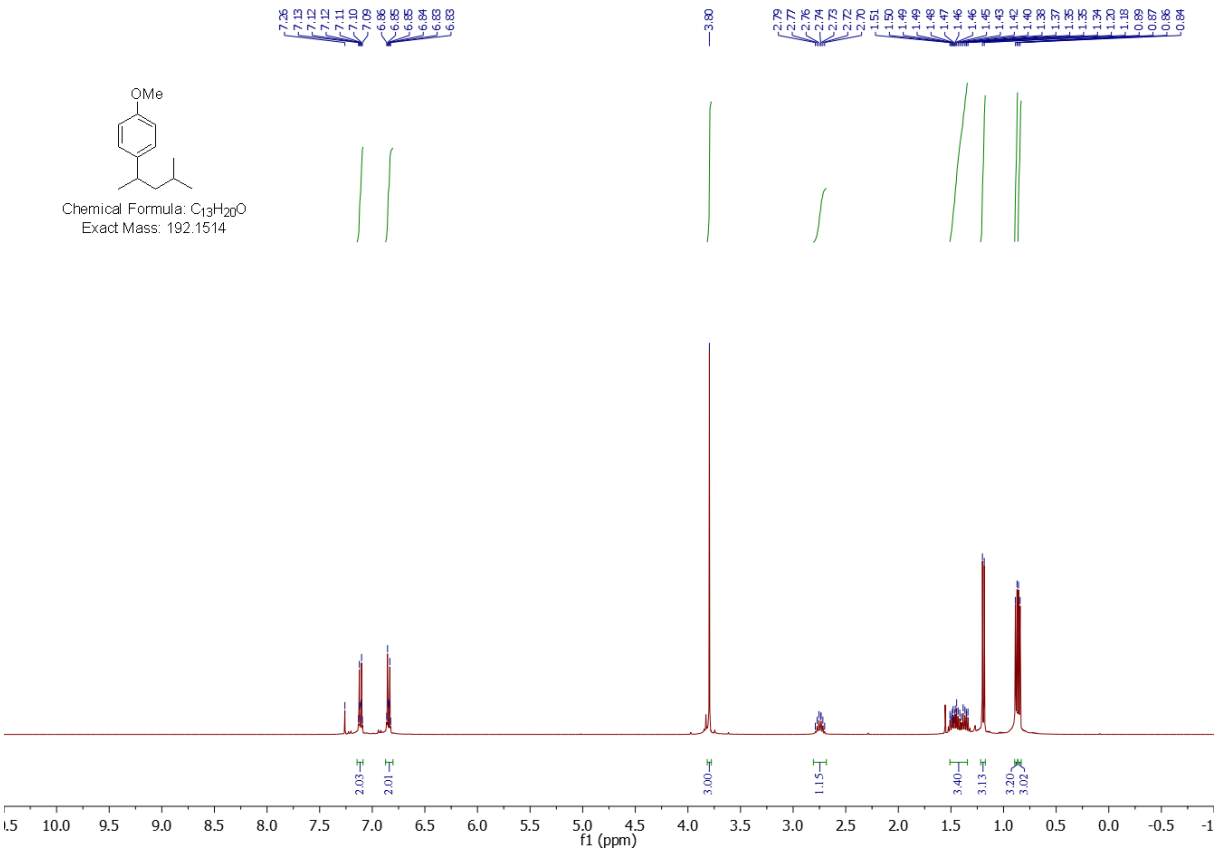

220.70
143.22
136.93
135.89
128.36
125.14
124.96
77.48
77.16
76.84
50.61
49.08
48.00
44.38
38.25
35.85
31.70
29.51
29.13
26.71
25.71
21.62
13.90
12.32
O
H
H
Chemical Formula: C23H32O
Exact Mass: 324.2453
f1 (ppm)

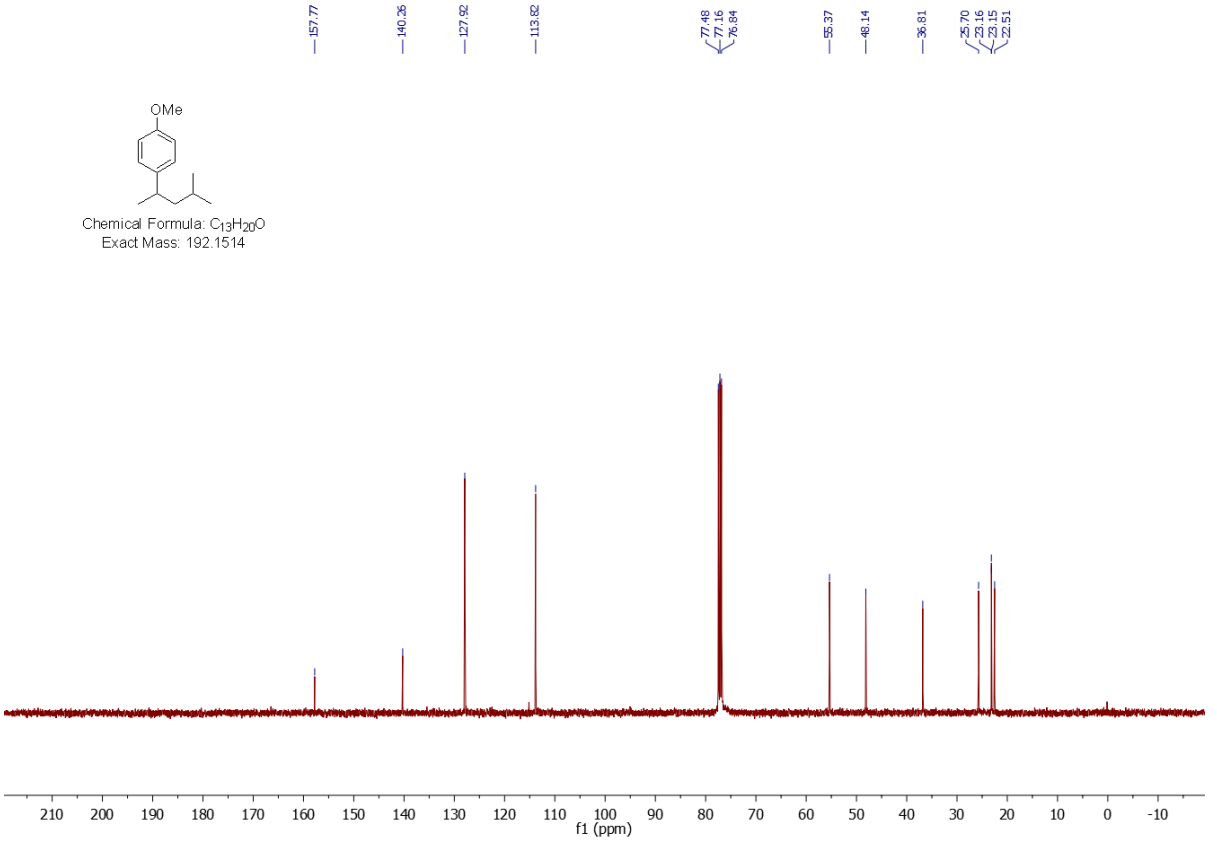

7.26
7.18
7.17
7.17
7.17
7.15
7.15
7.14
6.87
6.86
6.86
6.85
6.84
6.83
3.80
2.93
2.91
2.89
2.87
2.86
2.84
2.82
1.25
1.23
OMe
Chemical Formula: C10H14O
Exact Mass: 150.1045
1.99
1.99
3.00
1.07
6.13
f1 (ppm)

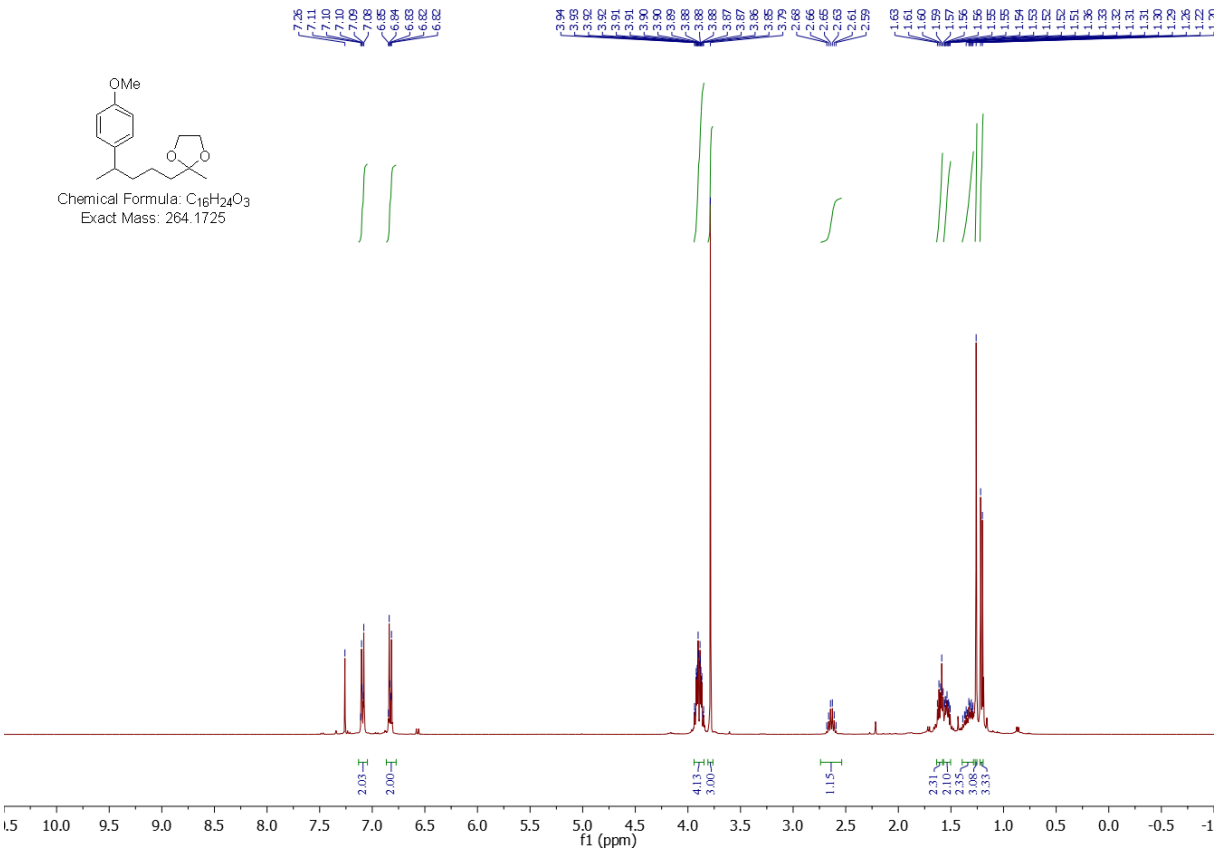

157.79
141.20
127.38
113.83
77.48
77.16
76.84
55.40
33.42
24.36
OMe
Chemical Formula: C10H14O
Exact Mass: 150.1045
f1 (ppm)

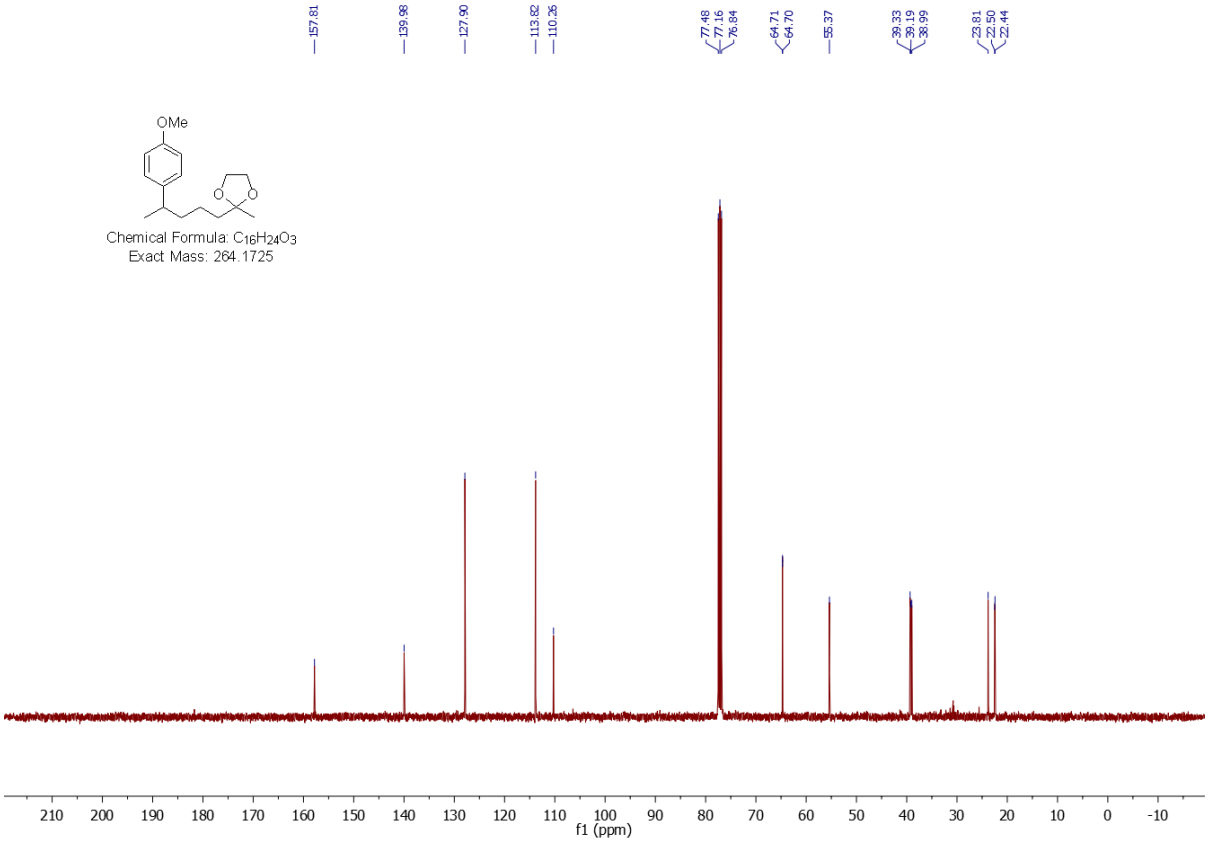

7.26
7.12
7.11
7.11
7.10
7.09
7.08
6.86
6.85
6.85
6.84
6.83
6.83
3.80
2.60
2.58
2.56
2.54
2.53
2.51
1.60
1.58
1.57
1.55
1.55
1.53
1.22
1.21
0.84
0.82
0.80
OMe
Chemical Formula: C11H16O
Exact Mass: 164.1201
1.92
1.91
3.00
1.05
2.41
3.22
3.17
f1 (ppm)

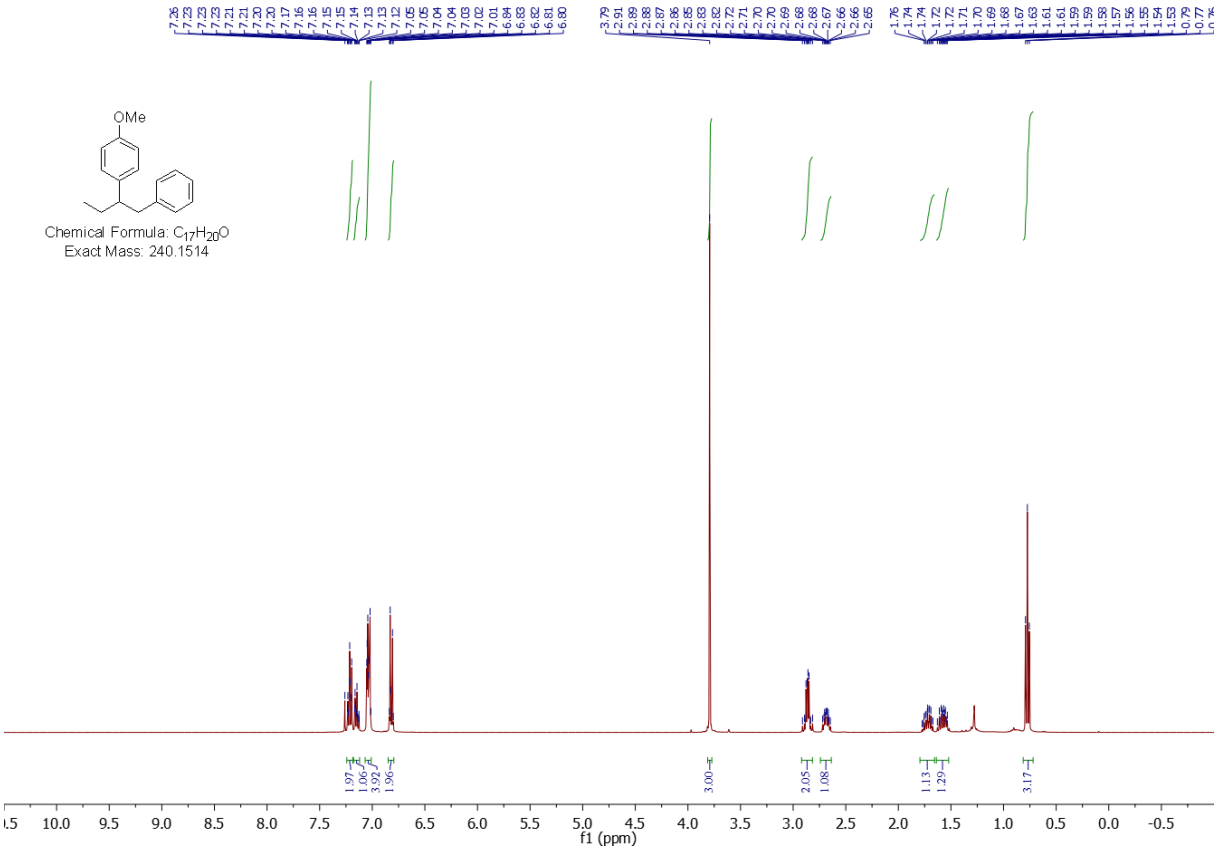

157.80
139.96
128.00
113.76
77.48
77.16
76.84
55.38
40.97
31.49
22.18
12.39
OMe
Chemical Formula: C11H16O
Exact Mass: 164.1201
f1 (ppm)


7.26
7.13
7.12
7.11
7.10
7.09
6.86
6.85
6.84
6.83
6.83
3.80
2.79
2.77
2.76
2.74
2.73
2.72
2.70
1.51
1.50
1.49
1.49
1.48
1.47
1.46
1.46
1.45
1.43
1.42
1.40
1.38
1.37
1.35
1.35
1.34
1.20
1.18
0.89
0.87
0.86
0.84
OMe
Chemical Formula: C13H20O
Exact Mass: 192.1514
2.03
2.01
3.00
1.15
3.40
3.13
3.20
3.02
f1 (ppm)


157.77
140.26
127.92
113.82
77.48
77.16
76.84
55.37
48.14
36.81
25.70
23.16
23.15
22.51
OMe
Chemical Formula: C13H20O
Exact Mass: 192.1514
f1 (ppm)


OMe
Chemical Formula: C16H24O3
Exact Mass: 264.1725
f1 (ppm)


OMe
Chemical Formula: C16H24O3
Exact Mass: 264.1725
157.81
139.98
127.90
113.82
110.26
77.48
77.16
76.84
64.71
64.70
55.37
39.33
39.19
38.99
23.81
22.50
22.44
f1 (ppm)


OMe
Chemical Formula: C17H20O
Exact Mass: 240.1514
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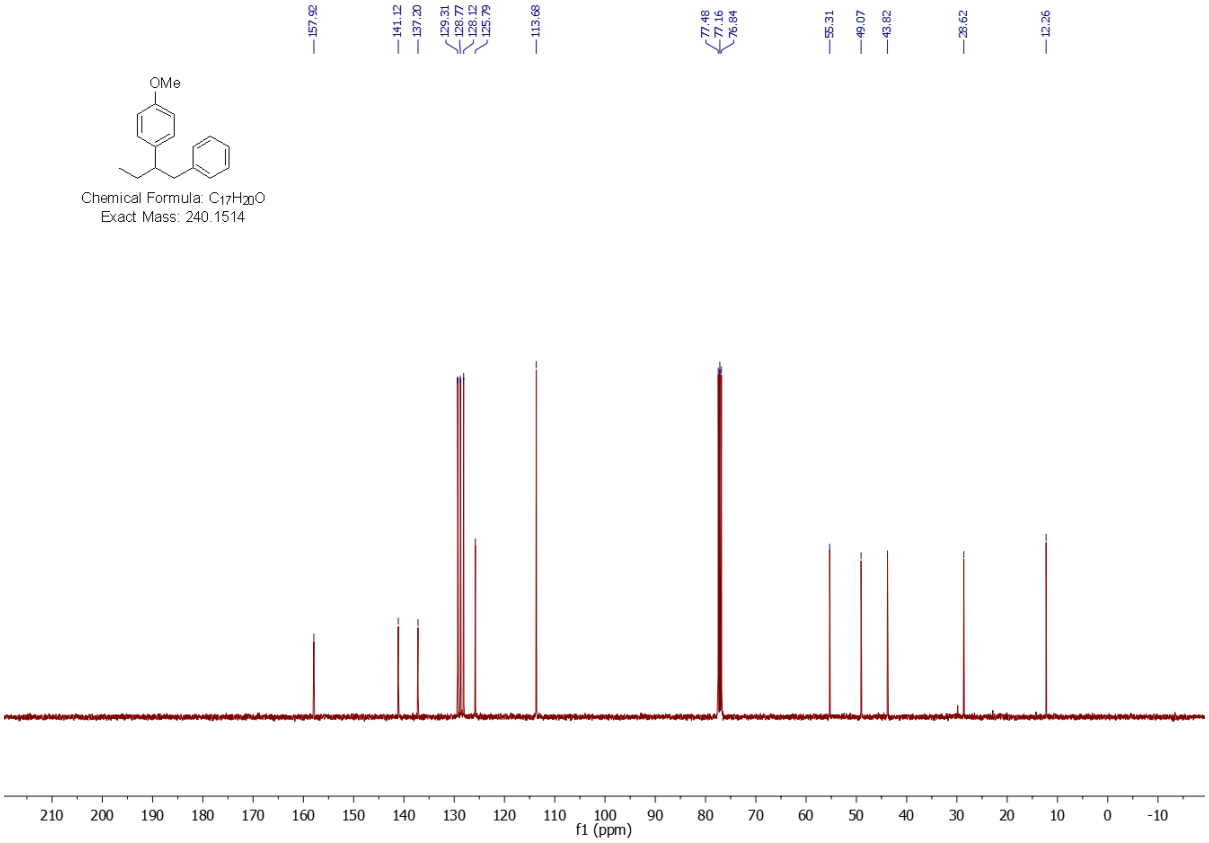
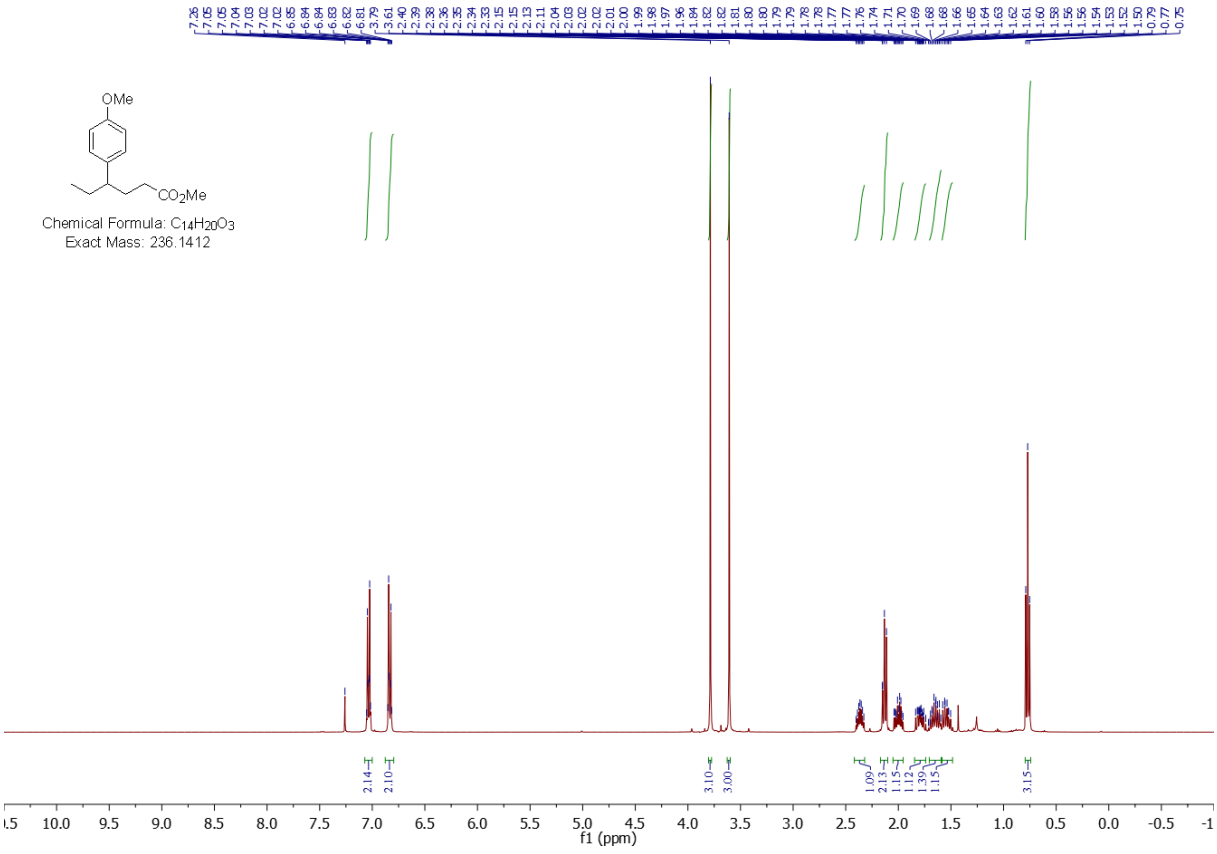
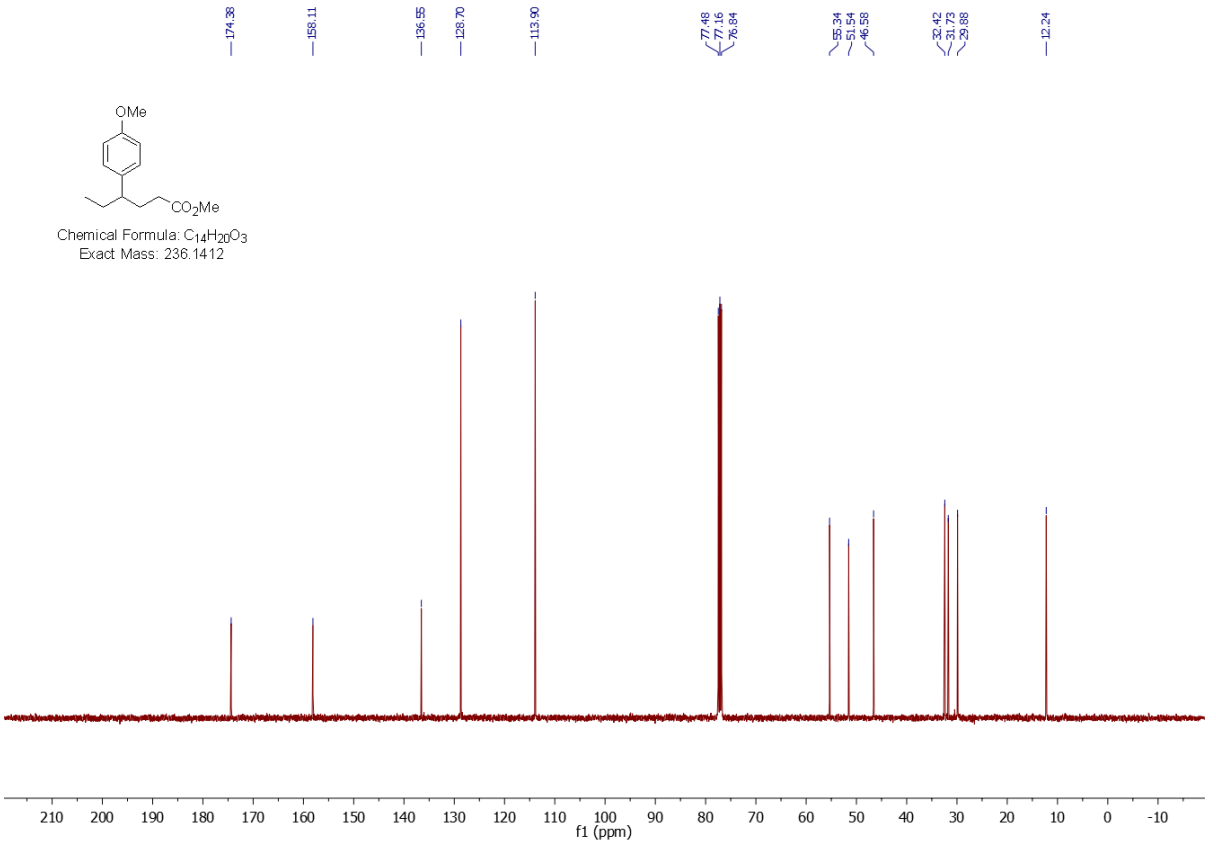
1.06
3.92
1.96
3.00
2.05
1.08
1.13
1.29
3.17
f1 (ppm)


157.92
141.12
137.20
129.31
128.77
128.12
125.79
113.68
77.48
77.16
76.84
55.31
49.07
43.82
28.62
12.26
OMe
Chemical Formula: C17H20O
Exact Mass: 240.1514
f1 (ppm)


OMe
CO2Me
Chemical Formula: C14H20O3
Exact Mass: 236.1412
2.14
2.10
3.10
3.00
1.09
2.13
1.15
1.12
1.39
1.15
3.15
f1 (ppm)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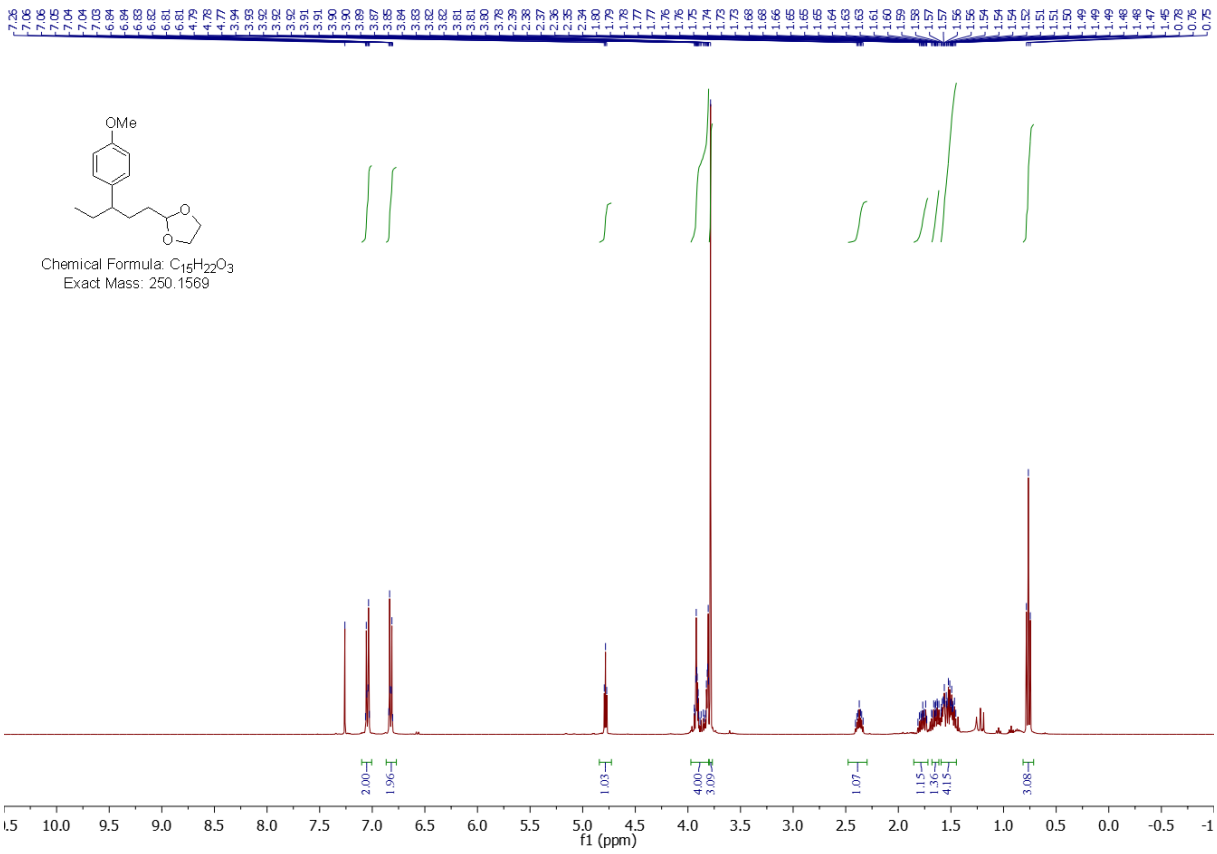
158.11
136.55
128.70
113.90
77.48
77.16
76.84
55.34
51.54
46.58
32.42
31.73
29.88
12.24
OMe
CO2Me
Chemical Formula: C14H20O3
Exact Mass: 236.1412
f1 (ppm)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Chemical Formula: C15H22O3
Exact Mass: 250.1569
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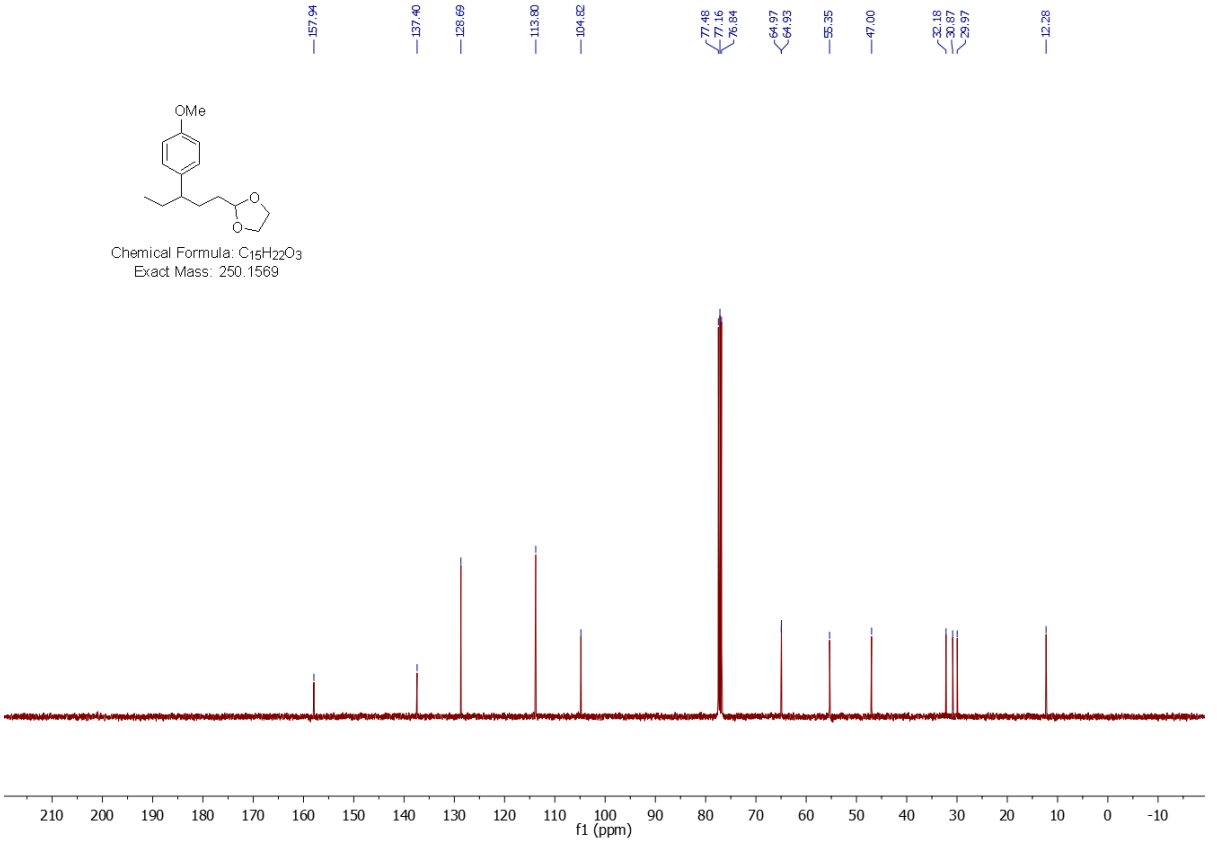
1.15
1.36
4.15
3.08
f1 (ppm)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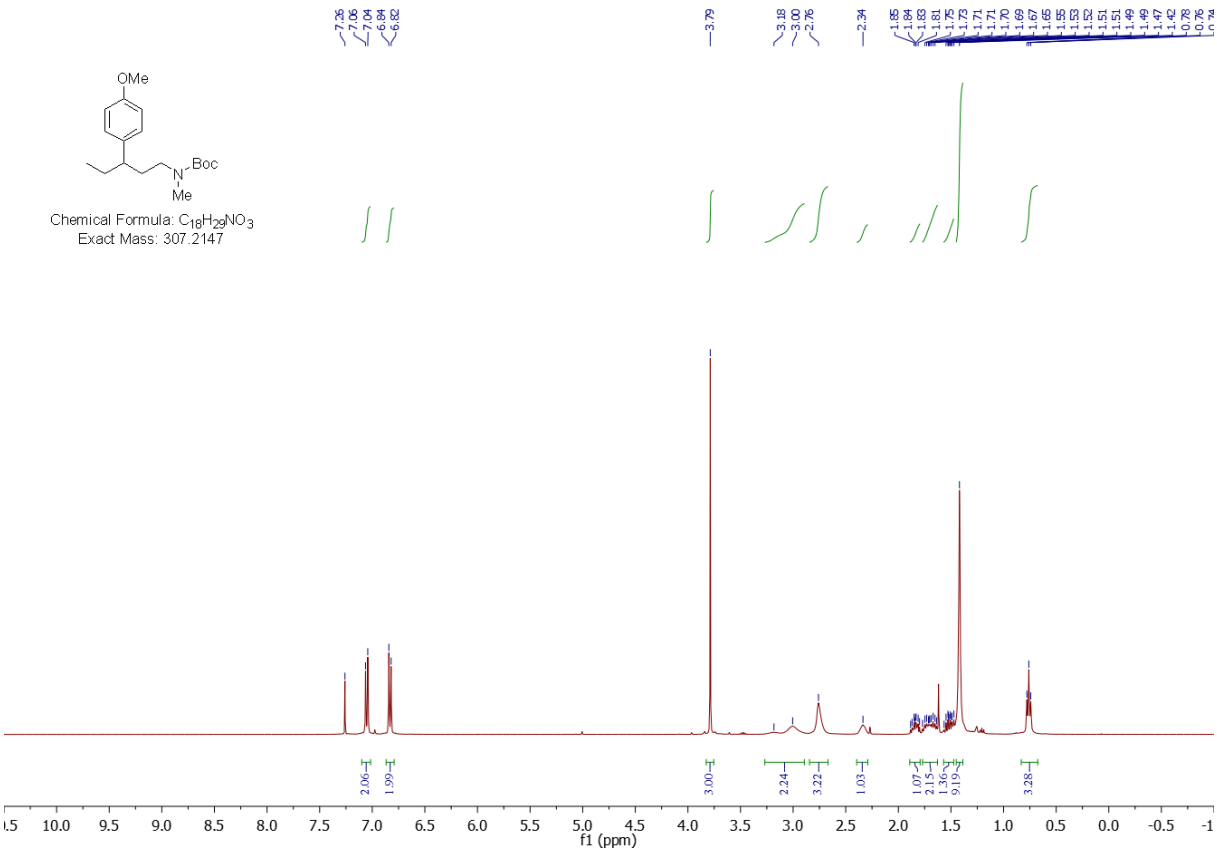
137.40
128.69
113.80
104.82
77.48
77.16
76.84
64.97
64.93
55.35
47.00
32.18
30.87
29.97
12.28
OMe
Chemical Formula: C15H22O3
Exact Mass: 250.1569
f1 (ppm)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3.79
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3.00
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1.85
1.84
1.83
1.81
1.75
1.73
1.71
1.71
1.70
1.69
1.67
1.65
1.55
1.53
1.52
1.51
1.49
1.47
1.42
0.78
0.76
OMe
Boc
N
Me
Chemical Formula: C18H29NO3
Exact Mass: 307.2147
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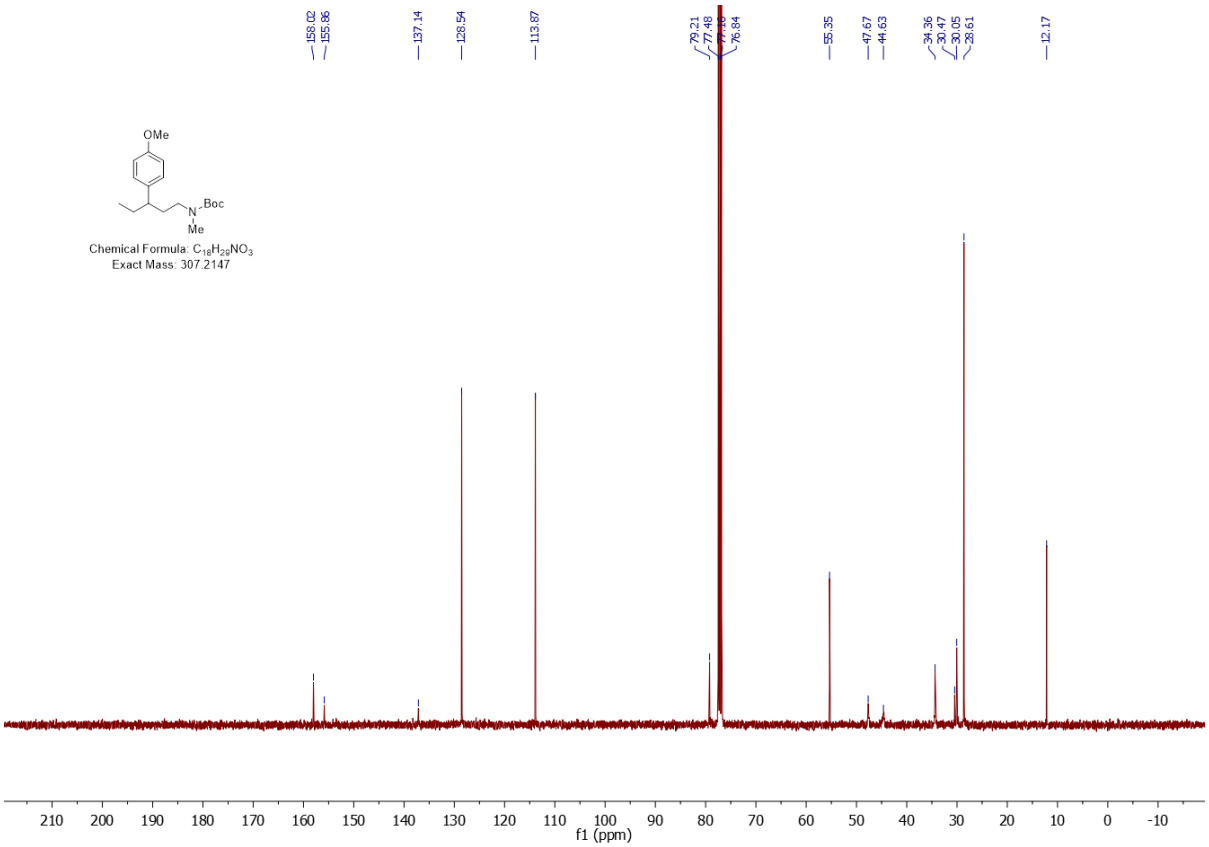
1.99
3.00
2.24
3.22
1.03
1.07
2.15
1.36
9.19
3.28
f1 (ppm)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137.14
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79.21
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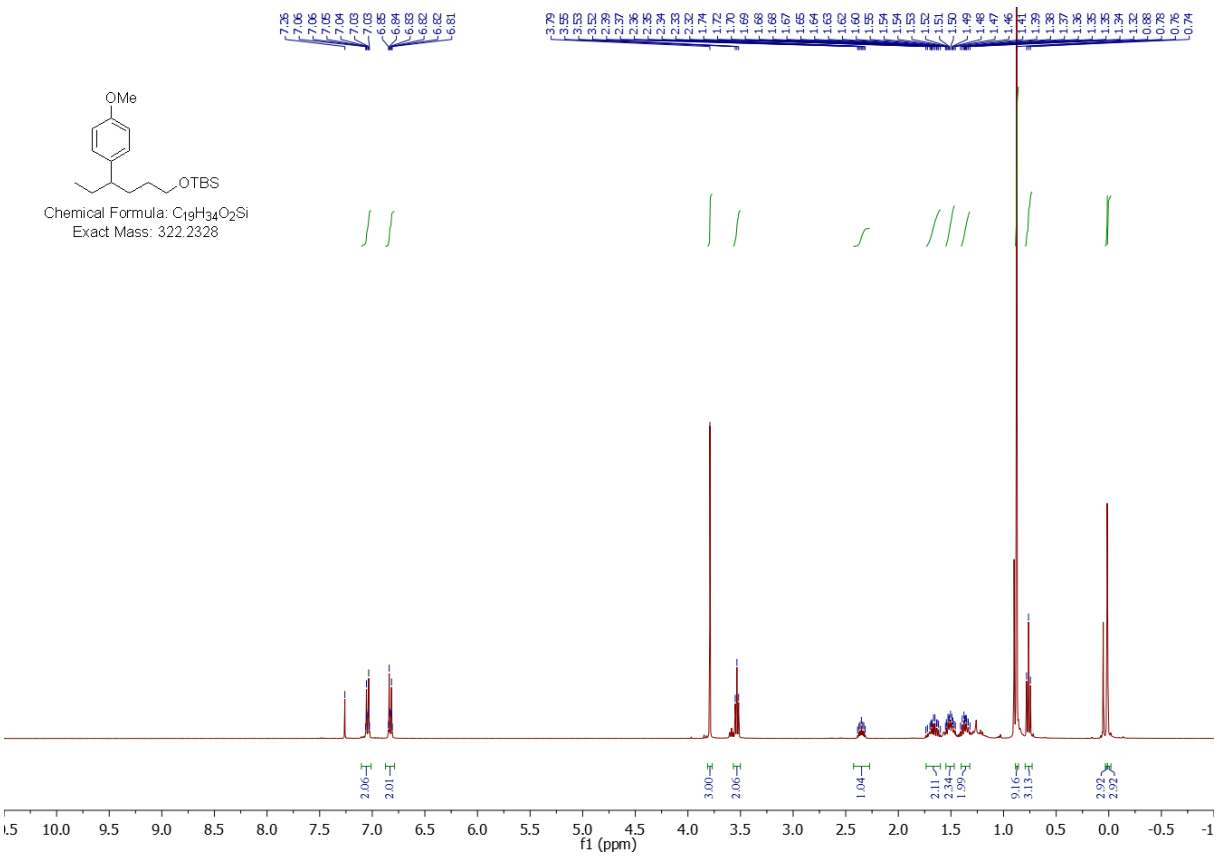
77.16
76.84
55.35
47.67
44.63
34.36
30.47
30.05
28.61
12.17
OMe
N
Boc
Me
Chemical Formula: C18H29NO3
Exact Mass: 307.2147
f1 (ppm)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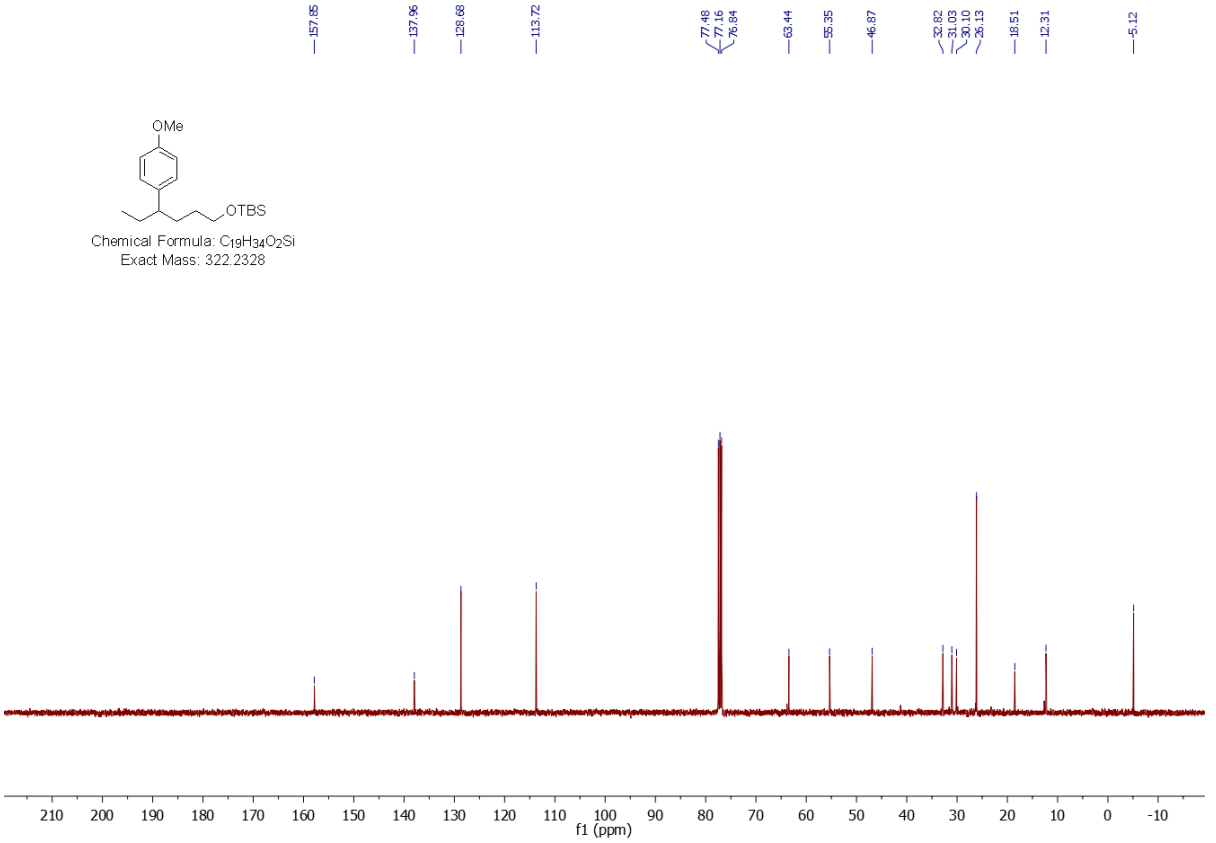
OTBS
Chemical Formula: C19H34O2Si
Exact Mass: 322.2328
f1 (ppm)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46.87
32.82
31.03
30.10
26.13
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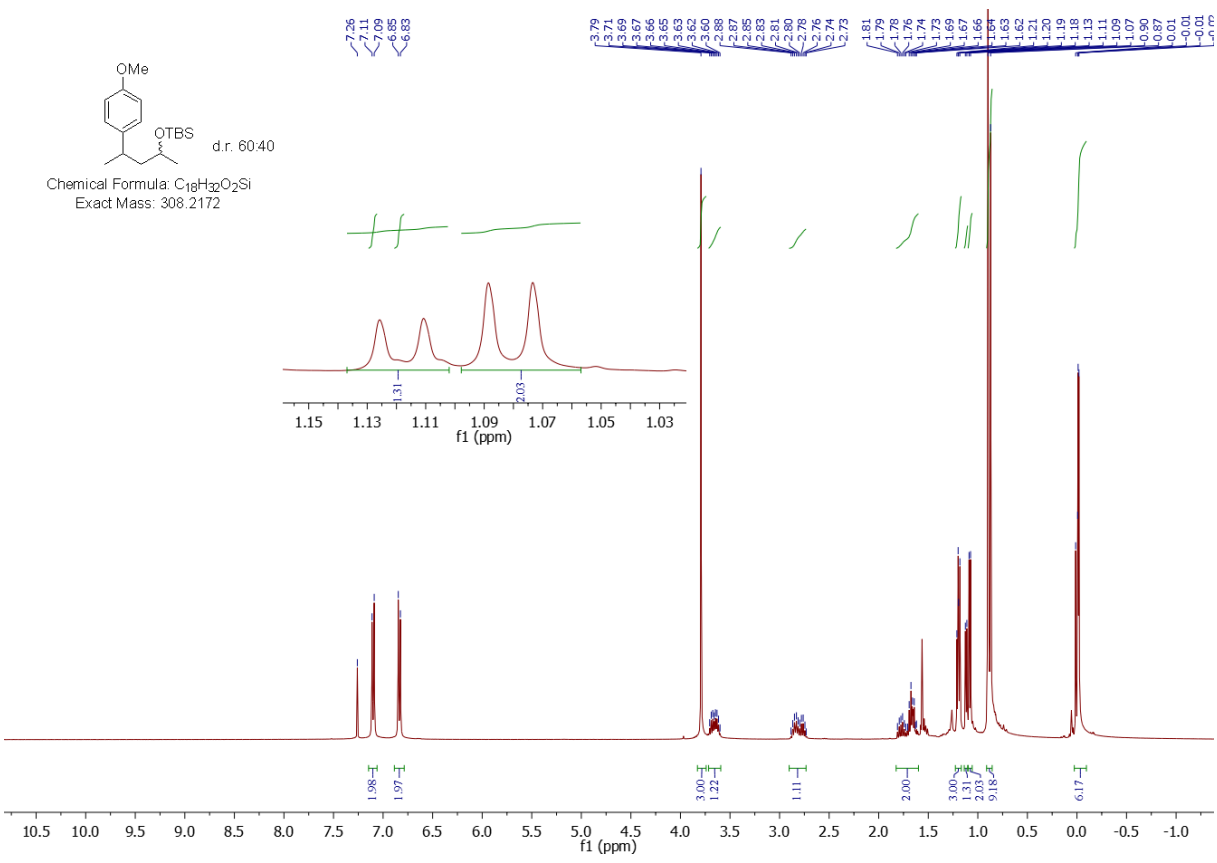
12.31
-5.12
OMe
OTBS
Chemical Formula: C19H34O2Si
Exact Mass: 322.2328
f1 (ppm)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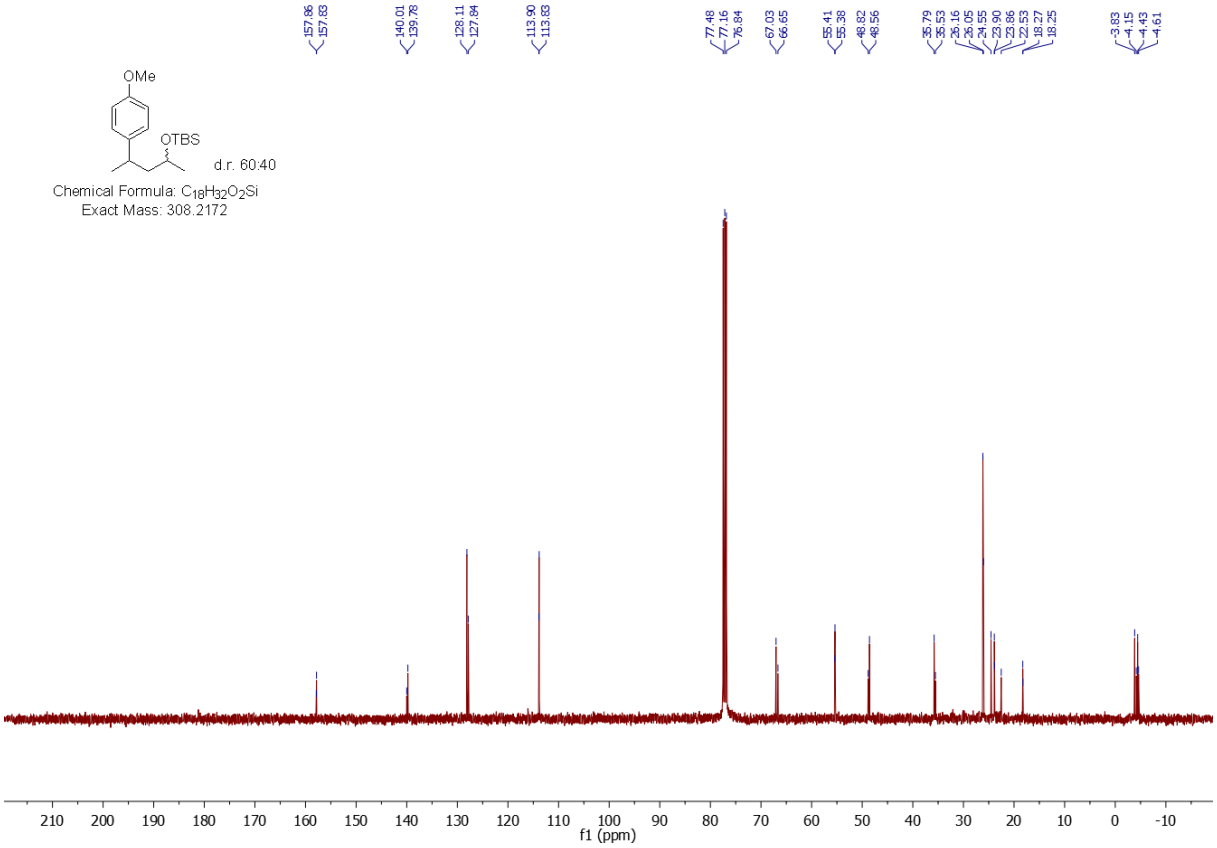
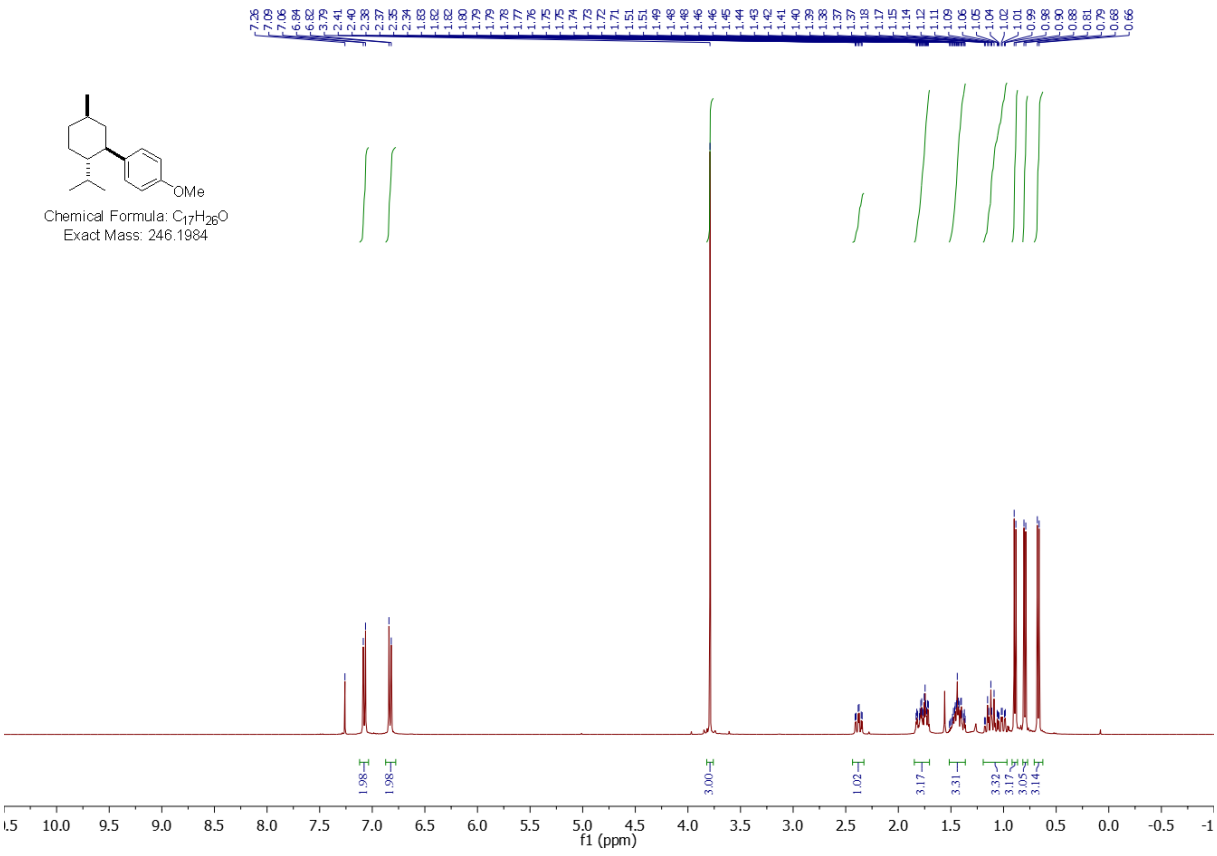
3.62
3.60
2.88
2.87
2.85
2.83
2.81
2.80
2.78
2.76
2.74
2.73
1.81
1.79
1.78
1.76
1.74
1.73
1.69
1.67
1.66
1.64
1.63
1.62
1.21
1.20
1.19
1.18
1.13
1.11
1.09
1.07
0.90
0.87
0.01
-0.01
OMe
OTBS
d.r. 60:40
Chemical Formula: C18H32O2Si
Exact Mass: 308.2172
1.31
2.03
f1 (ppm)
1.98
1.97
3.00
1.22
1.11
2.00
3.00
1.31
2.03
9.18
6.17
f1 (ppm)


OMe
OTBS
d.r. 60:40
Chemical Formula: C18H32O2Si
Exact Mass: 308.2172
f1 (ppm)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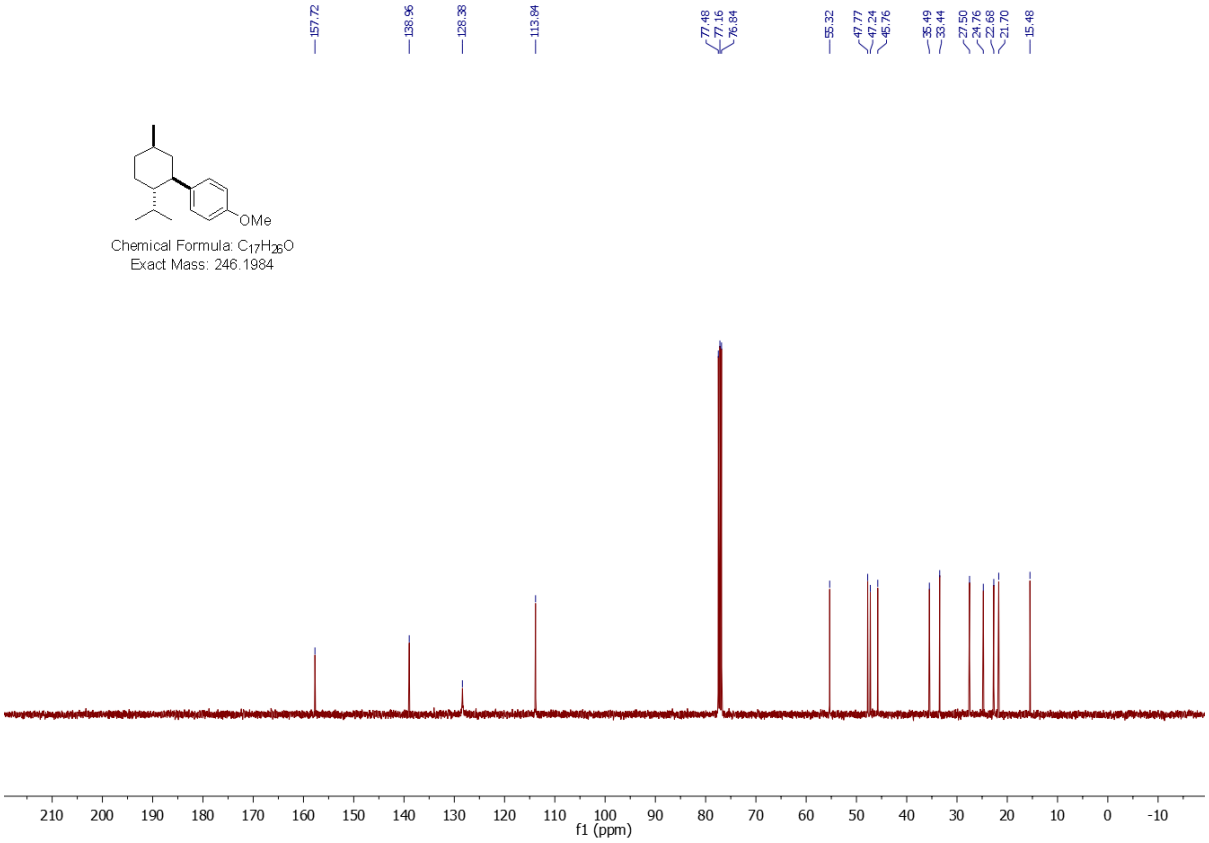
Chemical Formula: C17H26O
Exact Mass: 246.1984
f1 (ppm)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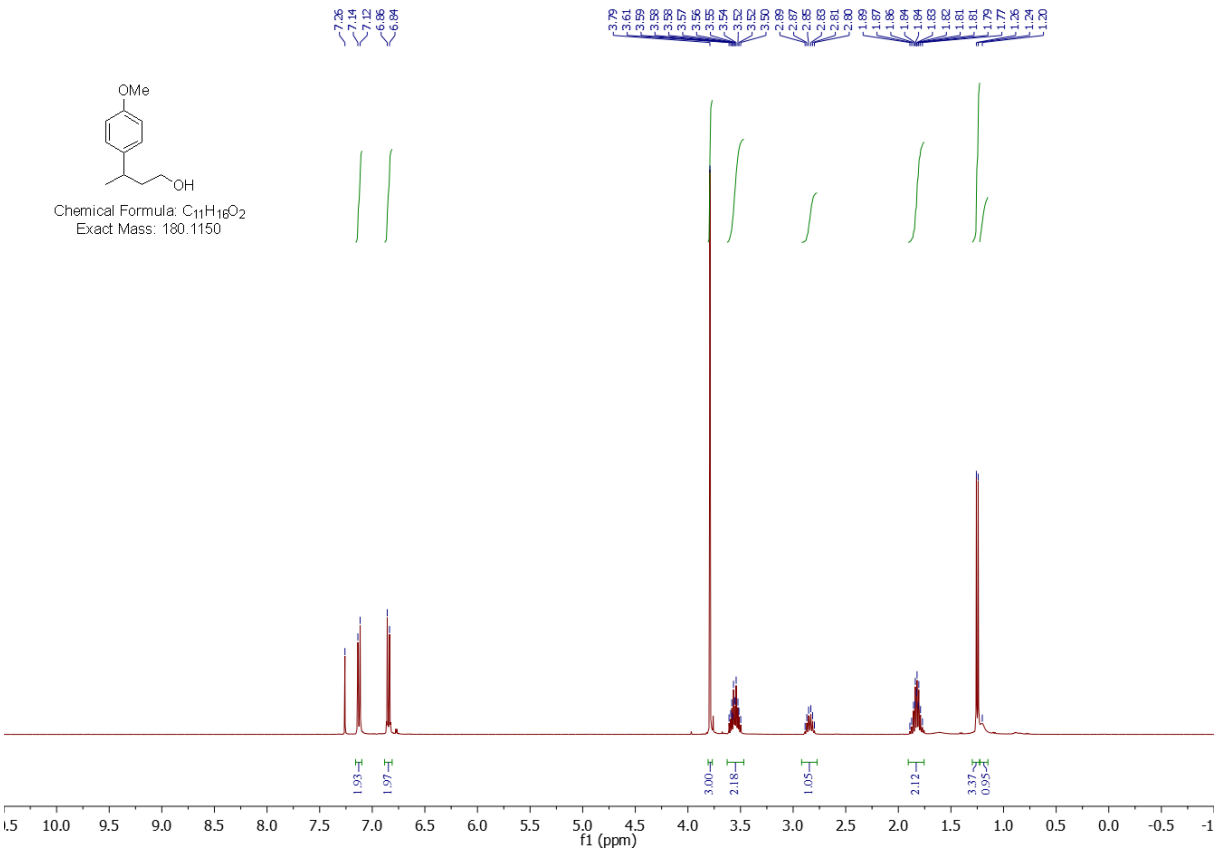
138.96
128.38
113.84
77.48
77.16
76.84
55.32
47.77
47.24
45.76
35.49
33.44
27.50
24.76
22.68
21.70
15.48
OMe
Chemical Formula: C17H26O
Exact Mass: 246.1984
f1 (ppm)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7.14
7.12
6.86
6.84
3.79
3.61
3.59
3.58
3.57
3.56
3.55
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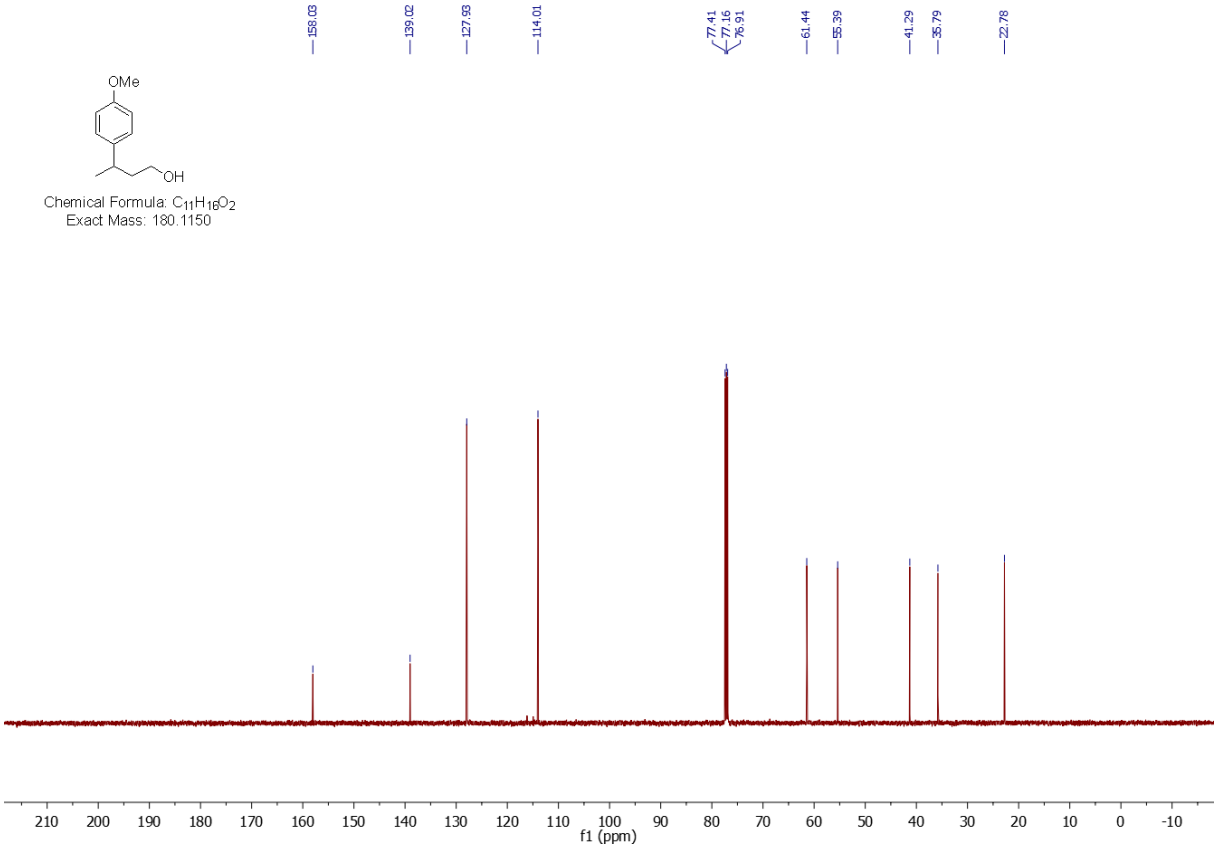
3.52
3.50
2.89
2.87
2.85
2.83
2.81
2.80
1.89
1.87
1.86
1.84
1.83
1.82
1.81
1.81
1.79
1.77
1.26
1.24
1.20
OMe
OH
Chemical Formula: C11H16O2
Exact Mass: 180.1150
1.93
1.97
3.00
2.18
1.05
2.12
3.37
0.95
f1 (ppm)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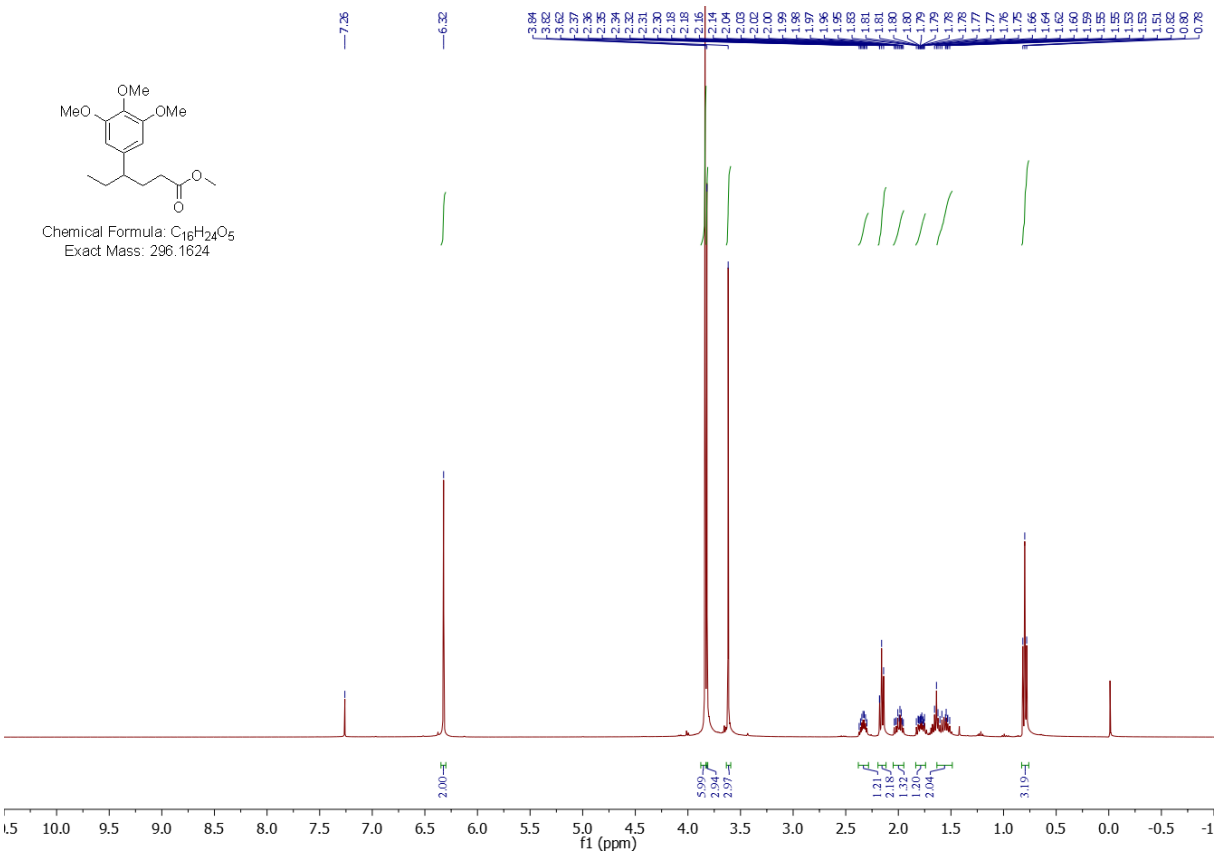
139.02
127.99
114.01
77.41
77.16
76.91
61.44
55.39
41.29
35.79
22.78
OMe
OH
Chemical Formula: C11H16O2
Exact Mass: 180.1150
f1 (ppm)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6.32
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MeO
OMe
O
O
Chemical Formula: C16H24O5
Exact Mass: 296.1624
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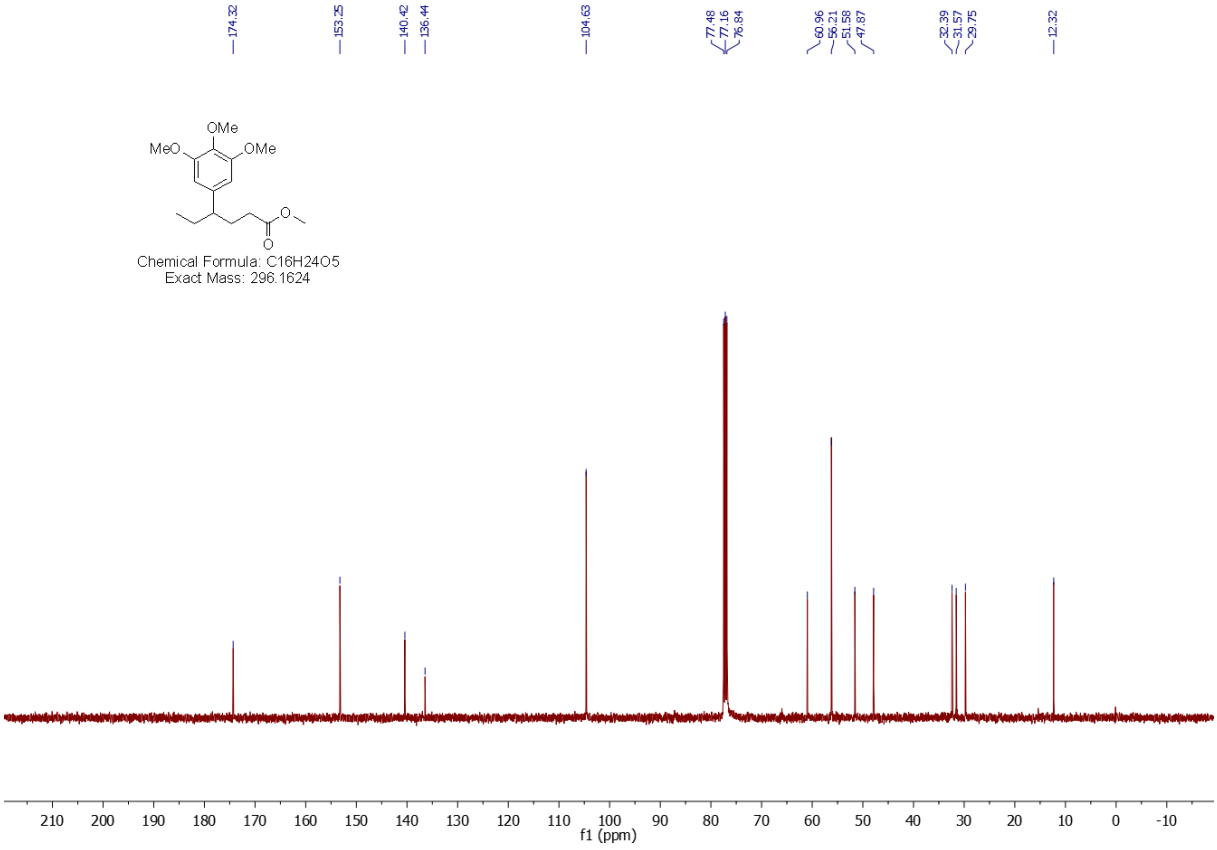
2.94
2.97
1.21
2.18
1.32
1.20
2.04
3.19
f1 (ppm)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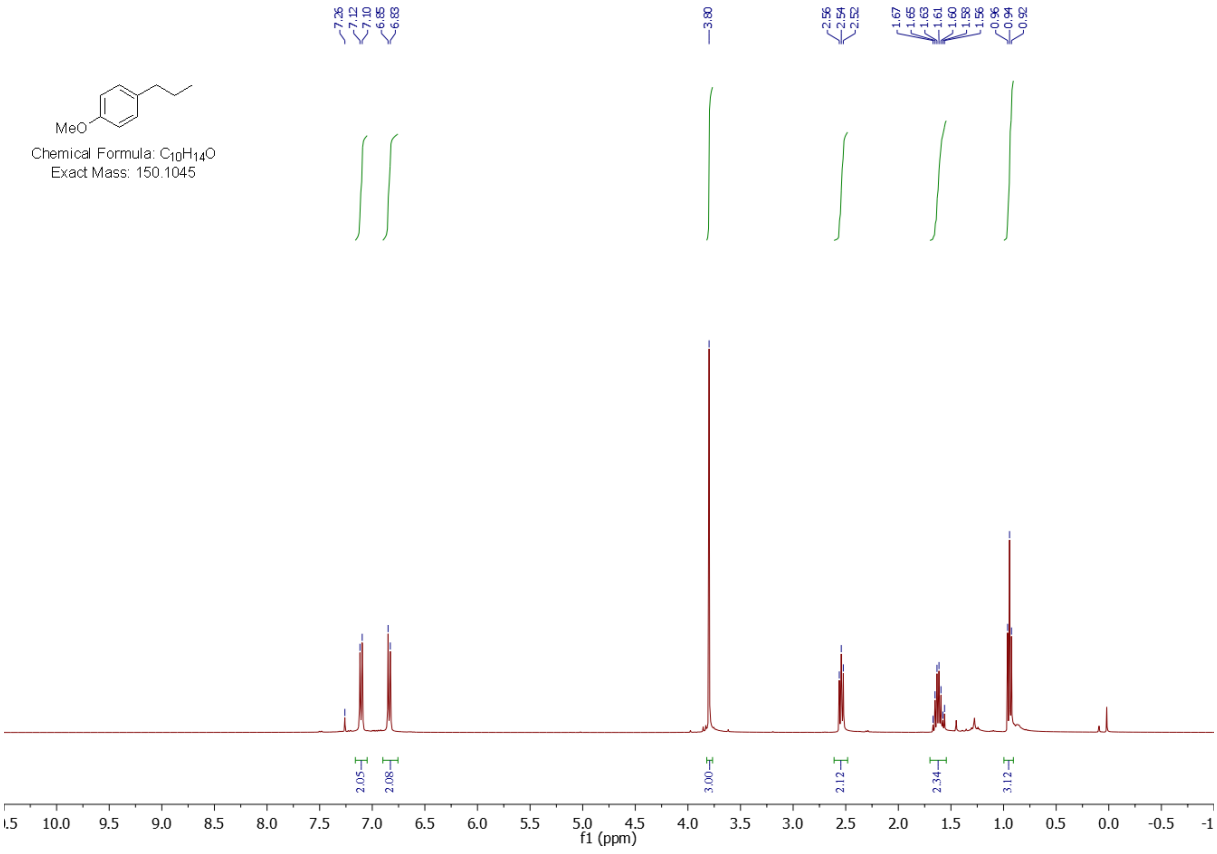
136.44
104.63
77.48
77.16
76.84
60.96
56.21
51.58
47.87
32.39
31.57
29.75
12.32
OMe
MeO
OMe
O
O
Chemical Formula: C16H24O5
Exact Mass: 296.1624
f1 (ppm)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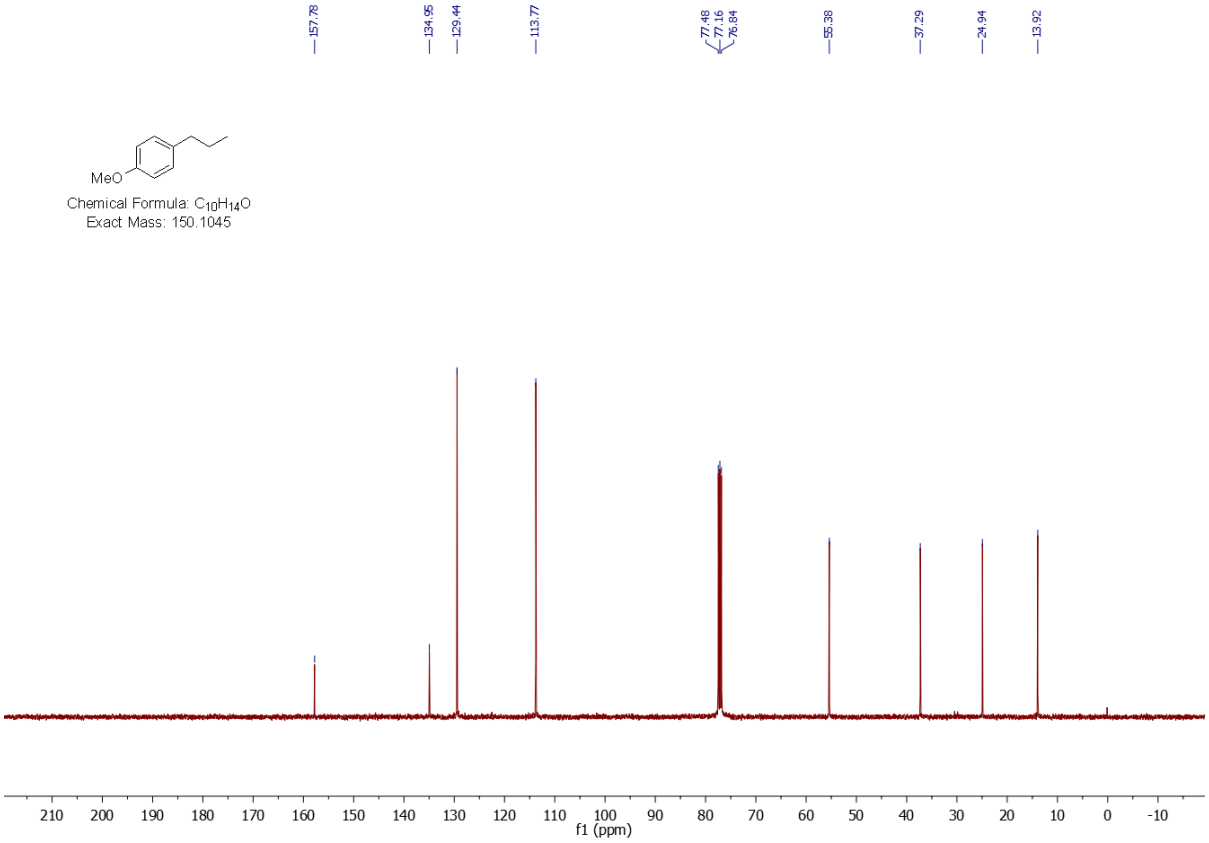
7.12
7.10
6.85
6.83
3.80
2.56
2.54
2.52
1.67
1.65
1.63
1.61
1.60
1.58
1.56
0.96
0.94
0.92
MeO
Chemical Formula: C10H14O
Exact Mass: 150.1045
2.05
2.08
3.00
2.12
2.34
3.12
f1 (ppm)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134.95
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113.77
77.48
77.16
76.84
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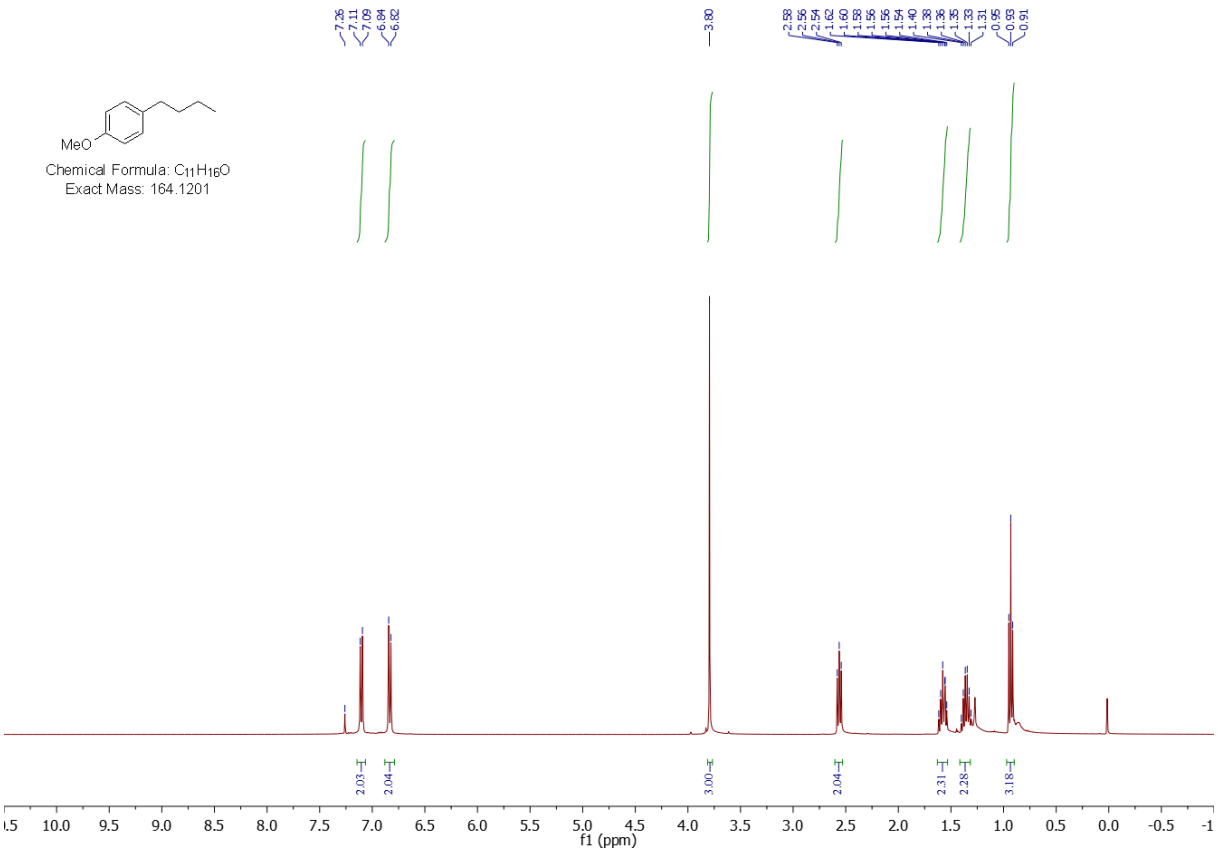
37.29
24.94
13.92
MeO
Chemical Formula: C10H14O
Exact Mass: 150.1045
f1 (ppm)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7.11
7.09
6.84
6.82
3.80
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2.56
2.54
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1.60
1.58
1.56
1.56
1.54
1.40
1.38
1.36
1.35
1.33
1.31
0.95
0.93
0.91
MeO
Chemical Formula: C11H16O
Exact Mass: 164.1201
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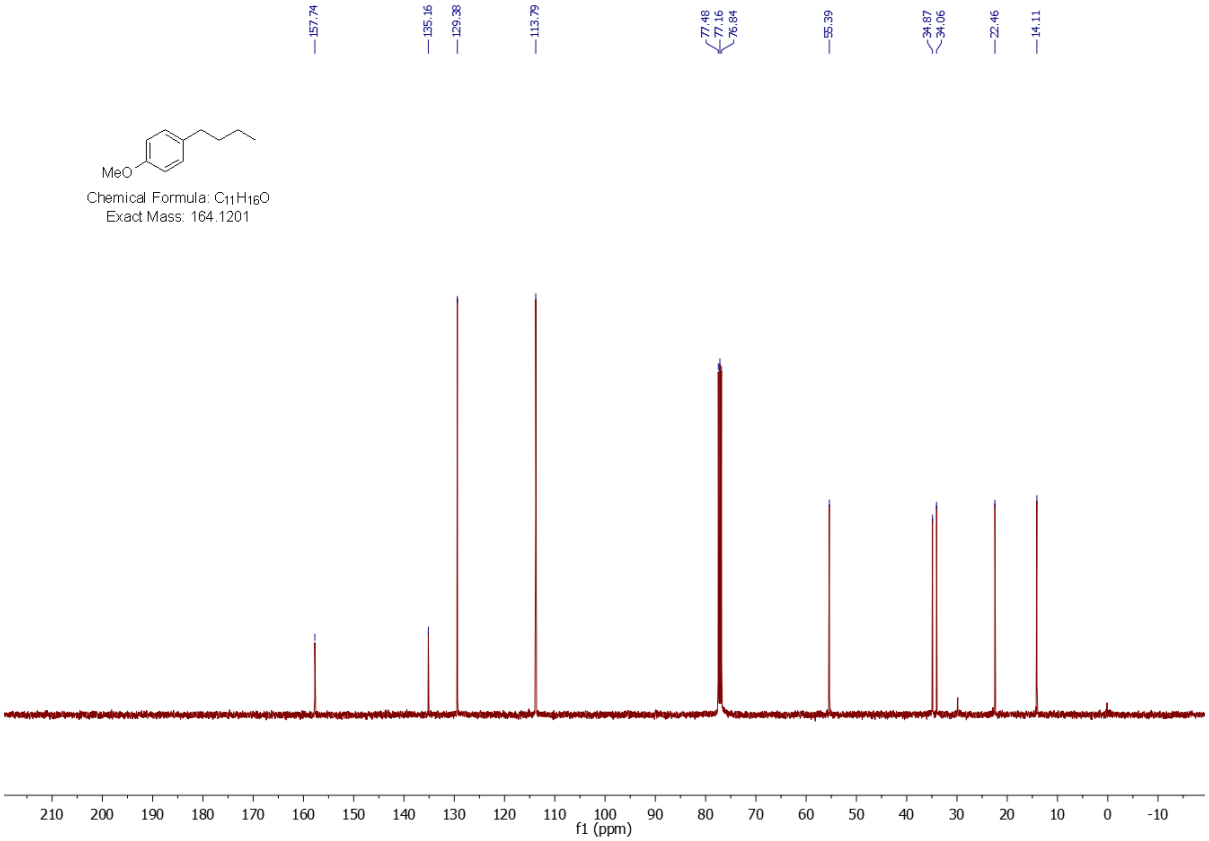
2.04
3.00
2.04
2.31
2.28
3.18
f1 (ppm)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77.16
76.84
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34.87
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14.11
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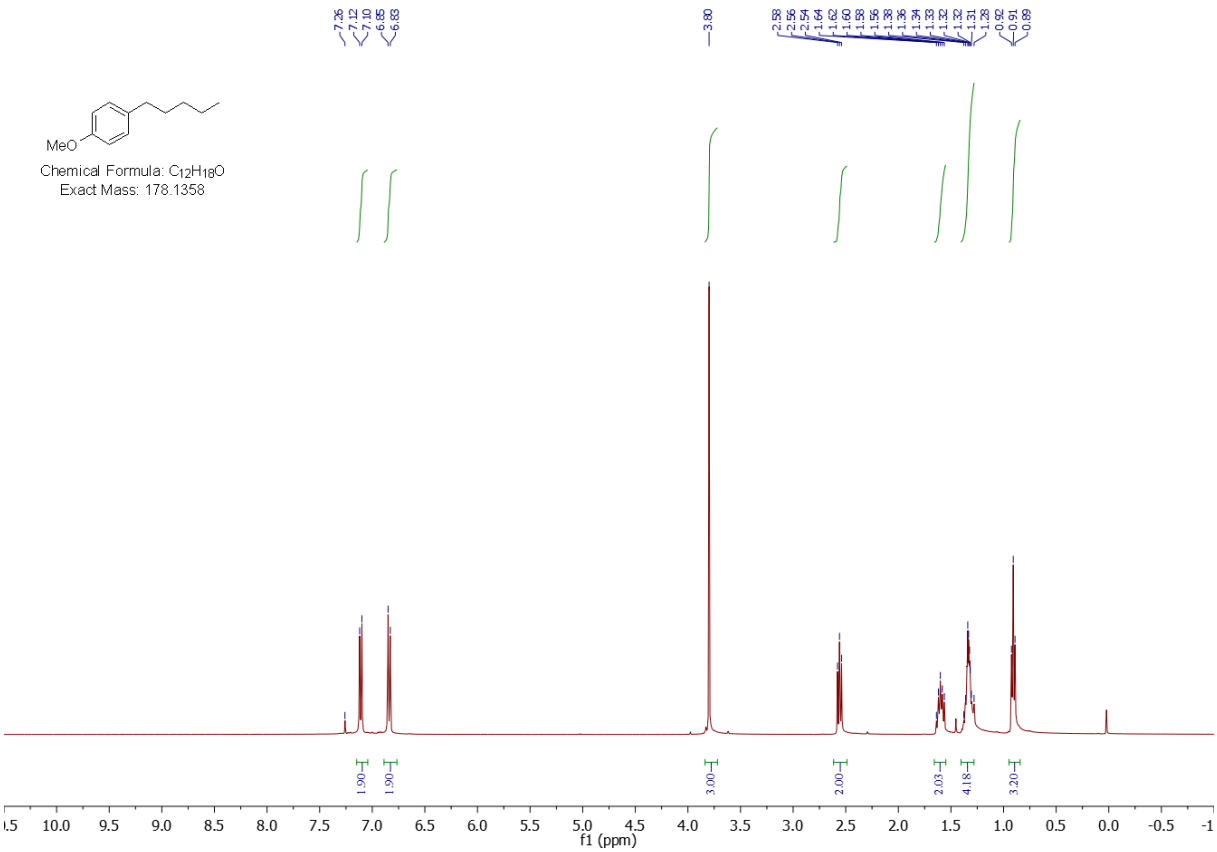
Chemical Formula: C11H16O
Exact Mass: 164.1201
f1 (ppm)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7.12
7.10
6.85
6.83
3.80
2.58
2.56
2.54
1.64
1.62
1.60
1.58
1.56
1.38
1.36
1.34
1.33
1.32
1.32
1.31
1.28
0.92
0.91
0.89
MeO
Chemical Formula: C12H18O
Exact Mass: 178.1358
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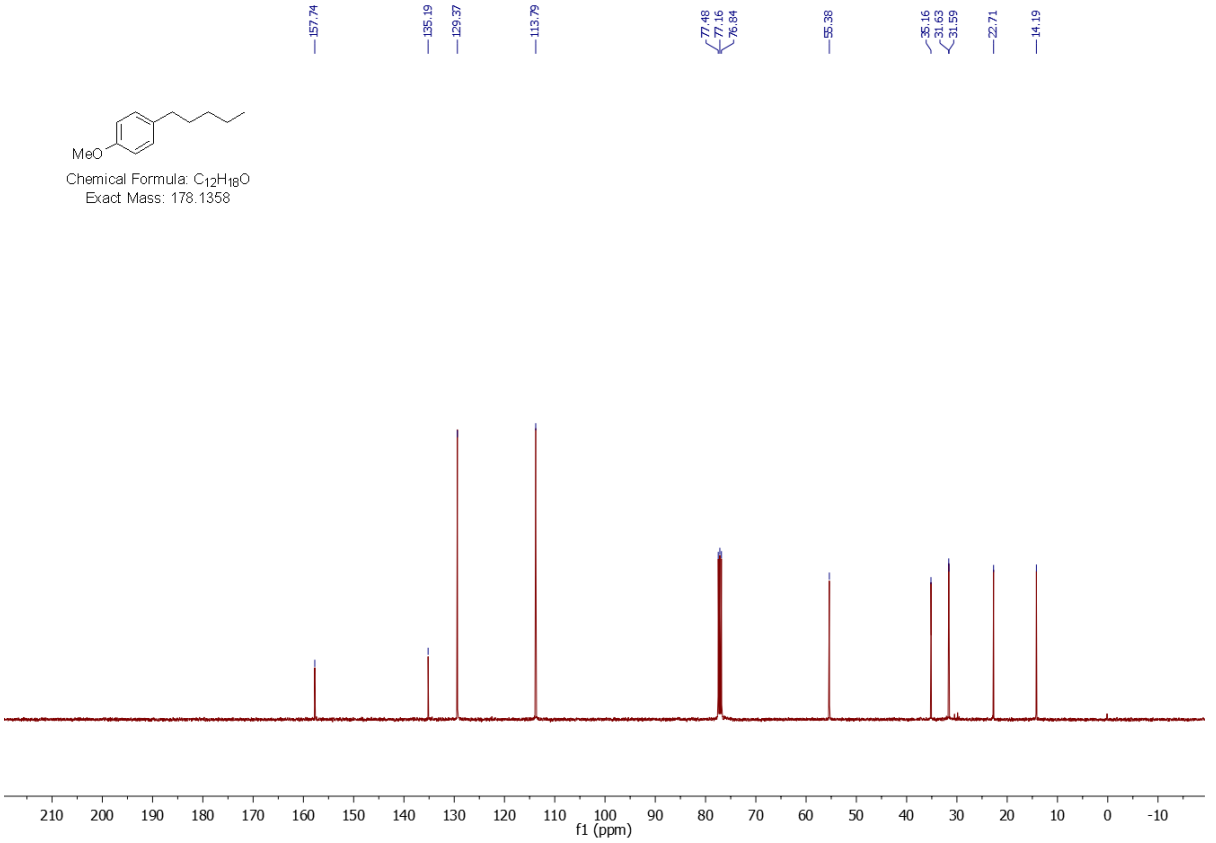
1.90
3.00
2.00
2.03
4.18
3.20
f1 (ppm)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76.84
55.38
35.16
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31.59
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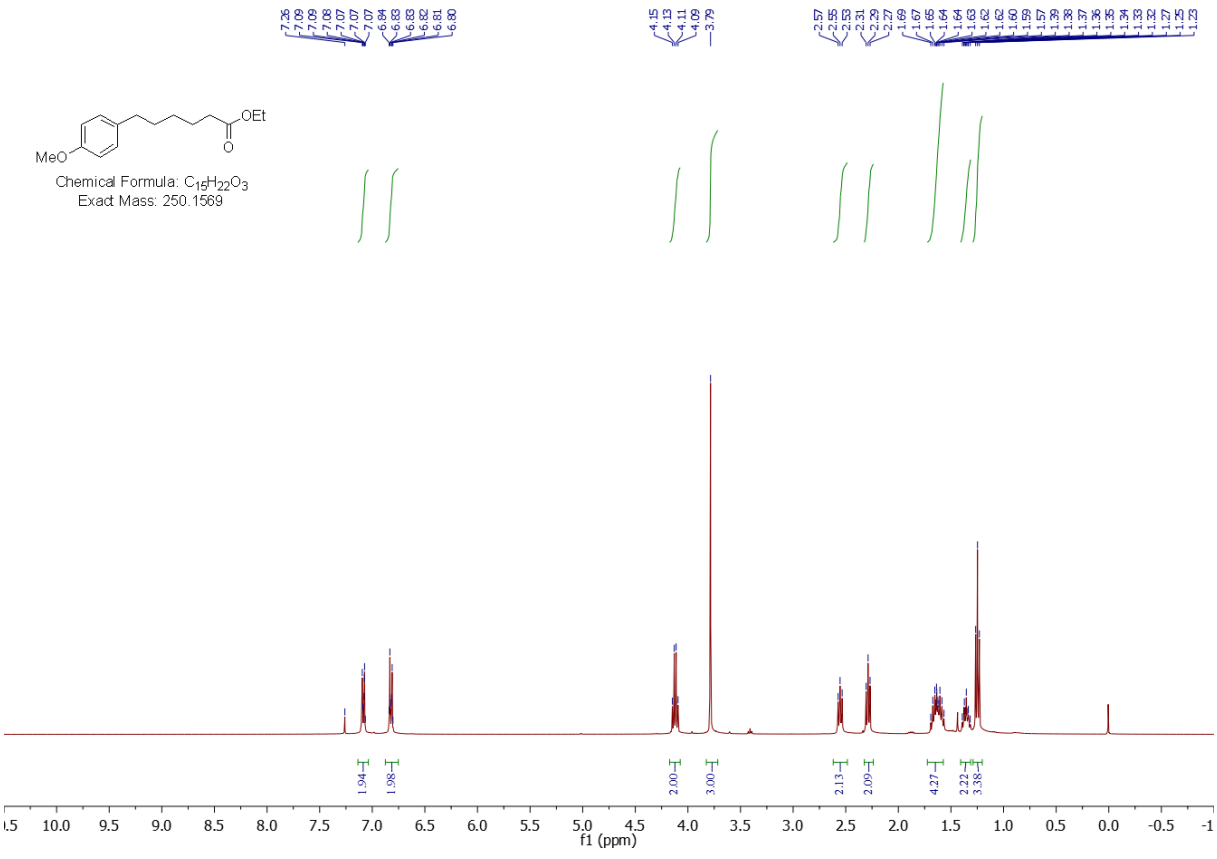
Exact Mass: 178.1358
f1 (ppm)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7.08
7.07
7.07
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6.83
6.82
6.81
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4.13
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1.39
1.38
1.37
1.36
1.35
1.34
1.33
1.32
1.27
1.25
1.23
OEt
O
MeO
Chemical Formula: C15H22O3
Exact Mass: 250.1569
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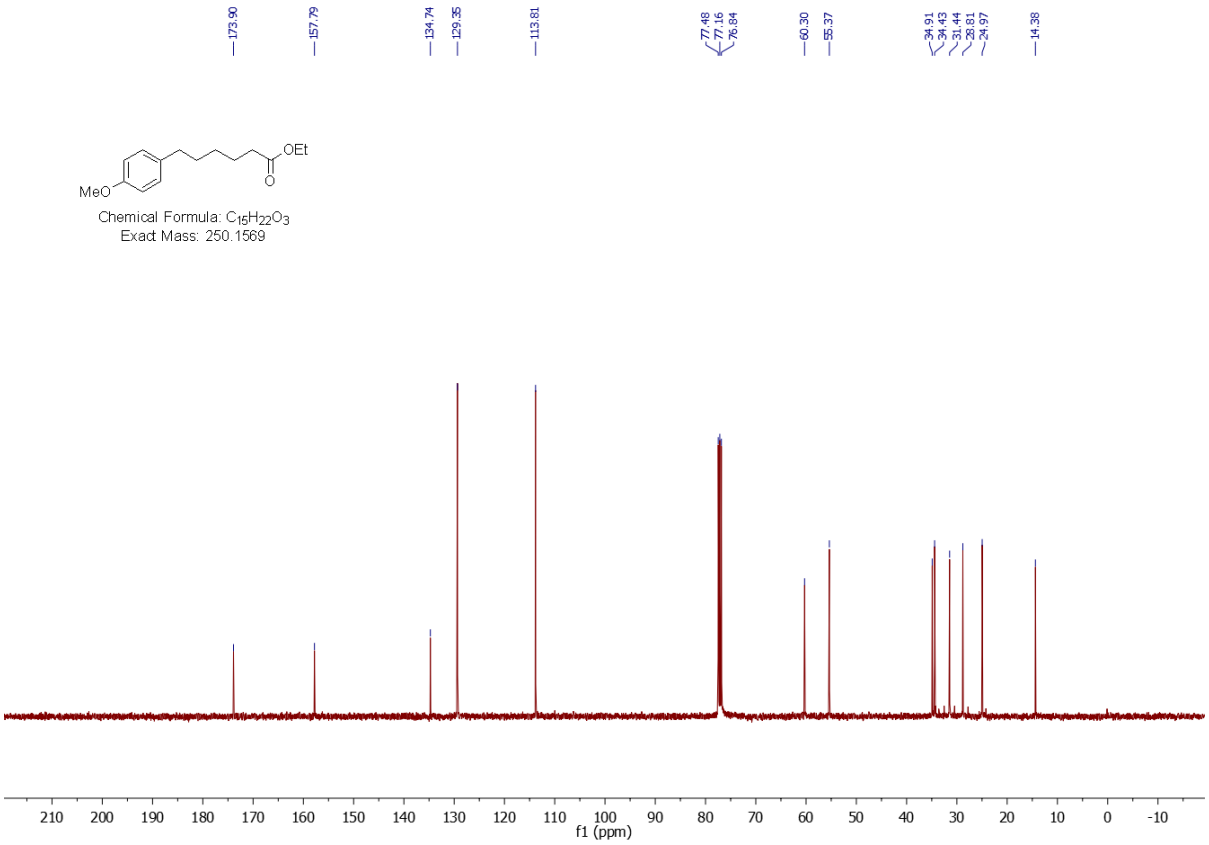
1.98
2.00
3.00
2.13
2.09
4.27
2.22
3.38
f1 (ppm)


173.90
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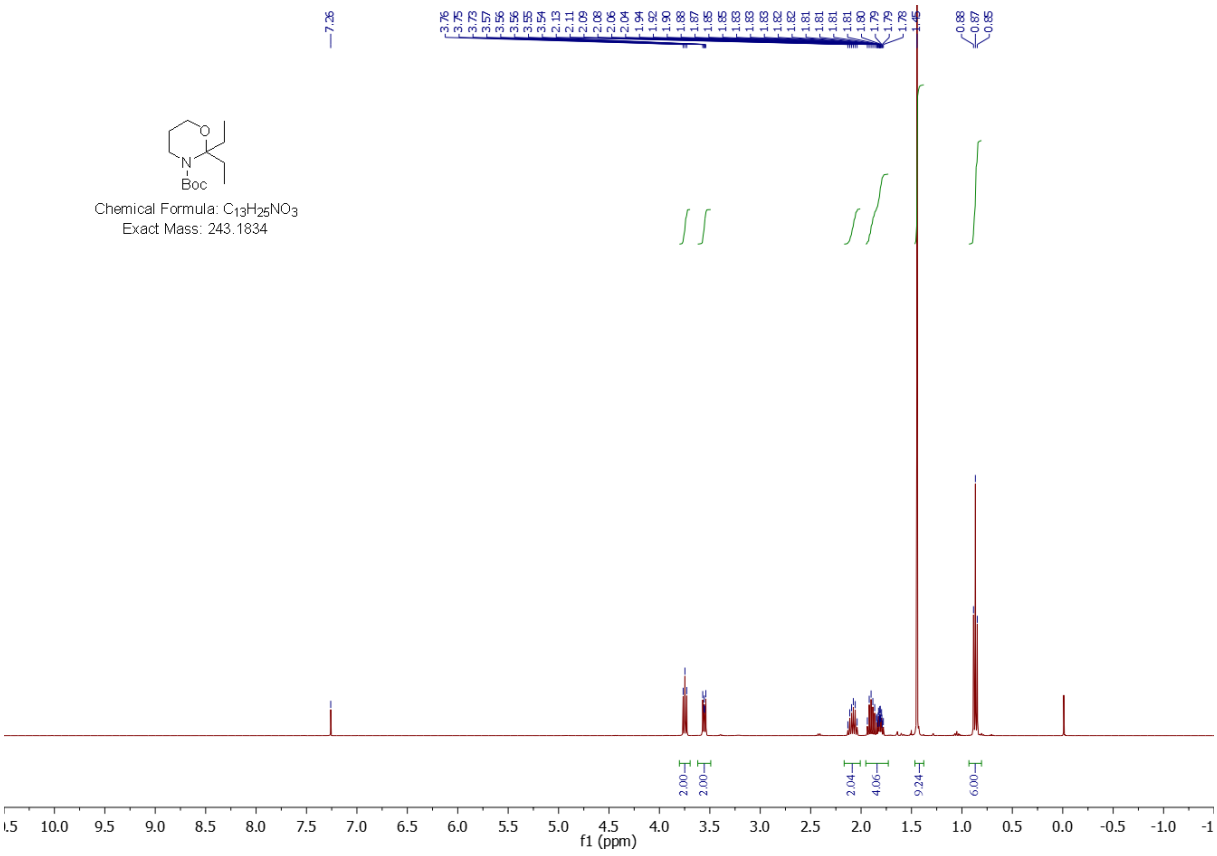
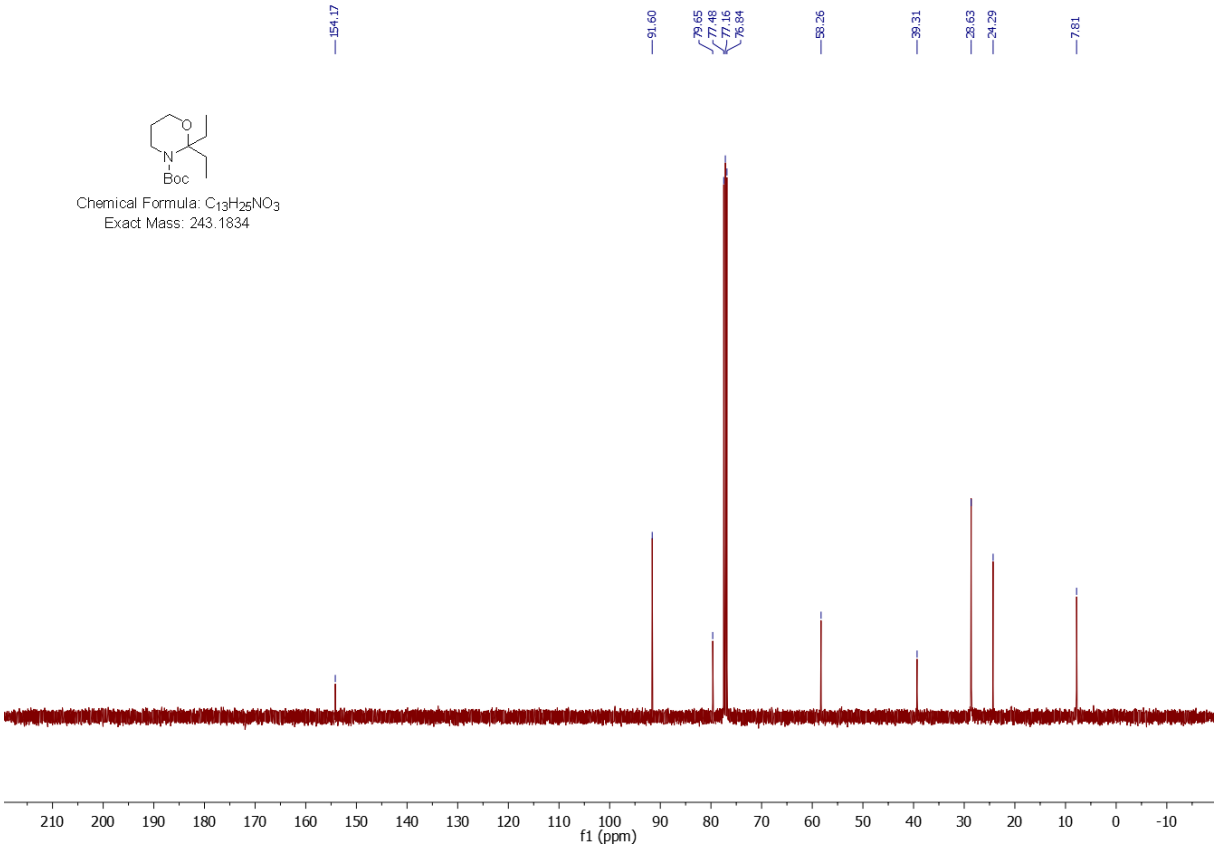
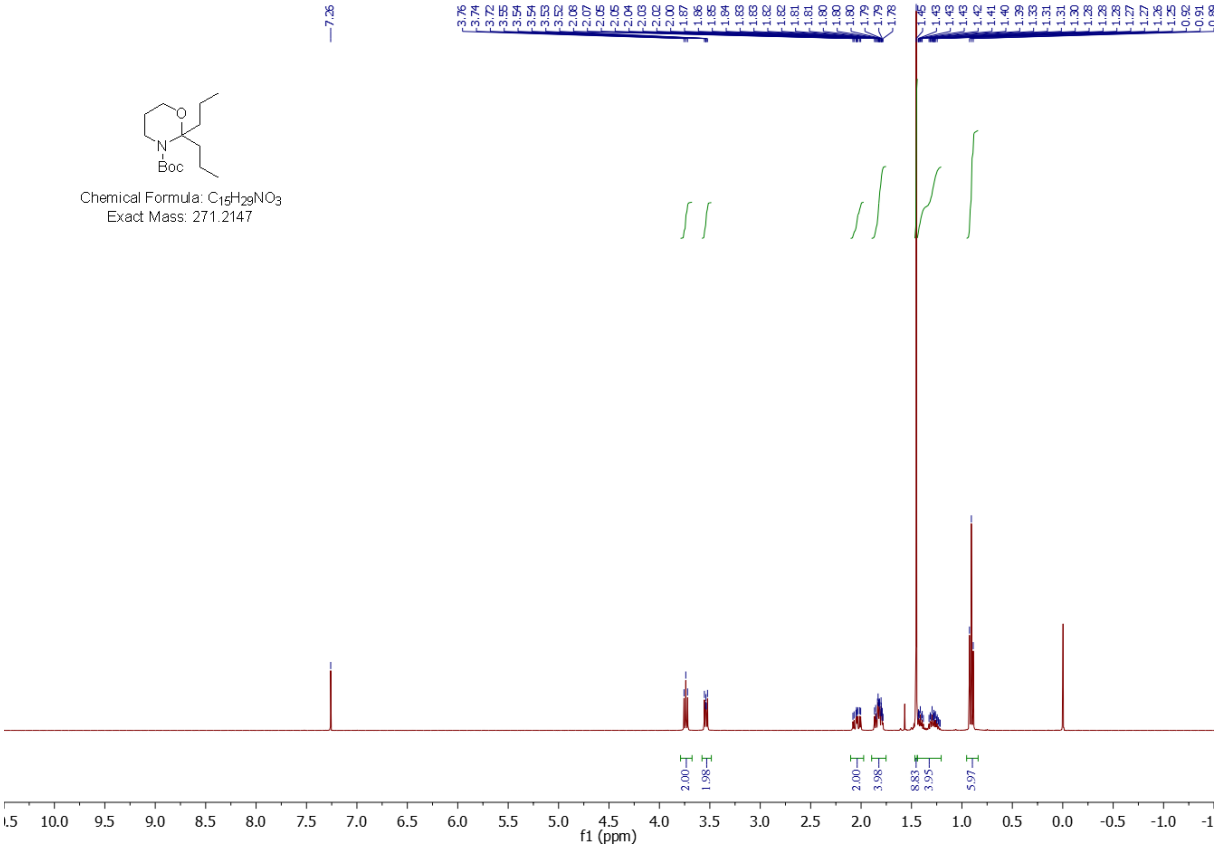
129.35
113.81
77.48
77.16
76.84
60.30
55.37
34.91
34.43
31.44
28.81
24.97
14.38
OEt
O
MeO
Chemical Formula: C15H22O3
Exact Mass: 250.1569
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

Chapter 4


Boc
Chemical Formula: C13H25NO3
Exact Mass: 243.1834
f1 (ppm)


Boc
Chemical Formula: C13H25NO3
Exact Mass: 243.1834
f1 (ppm)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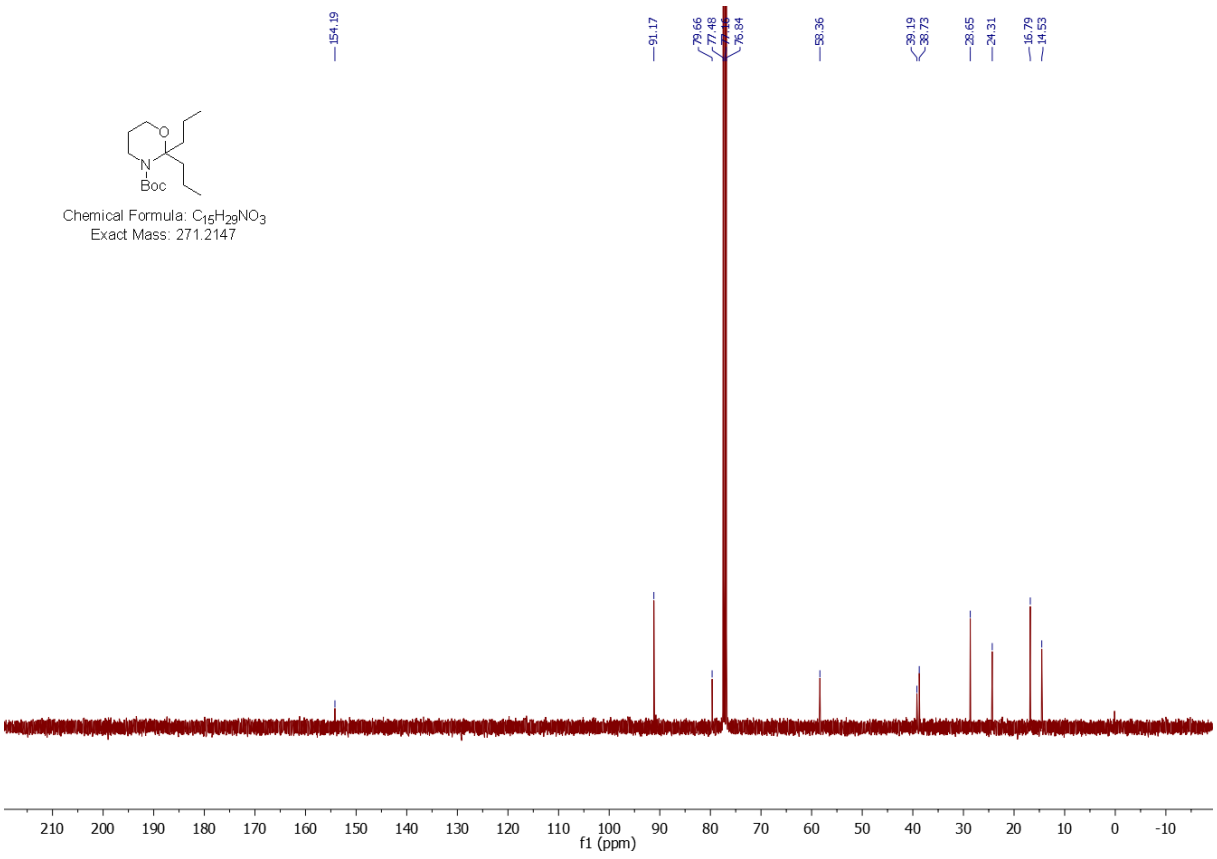
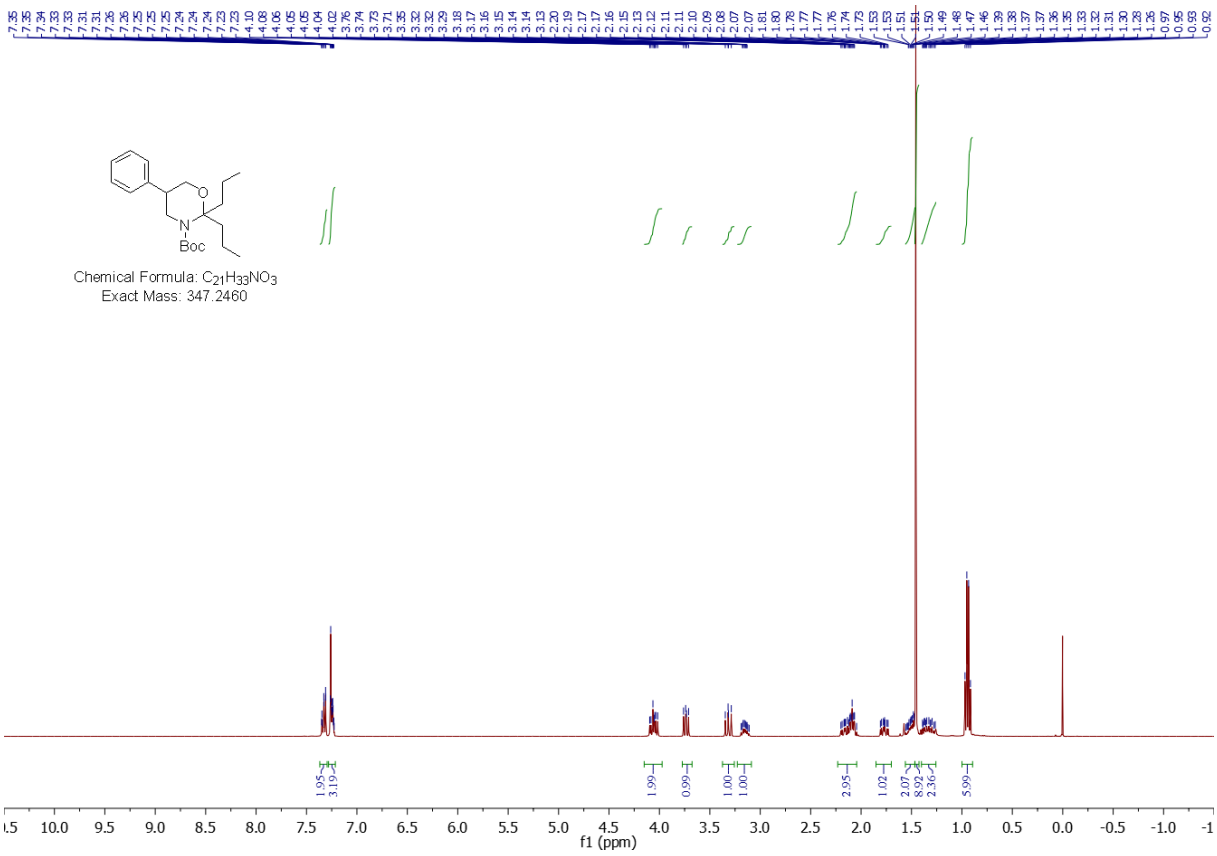
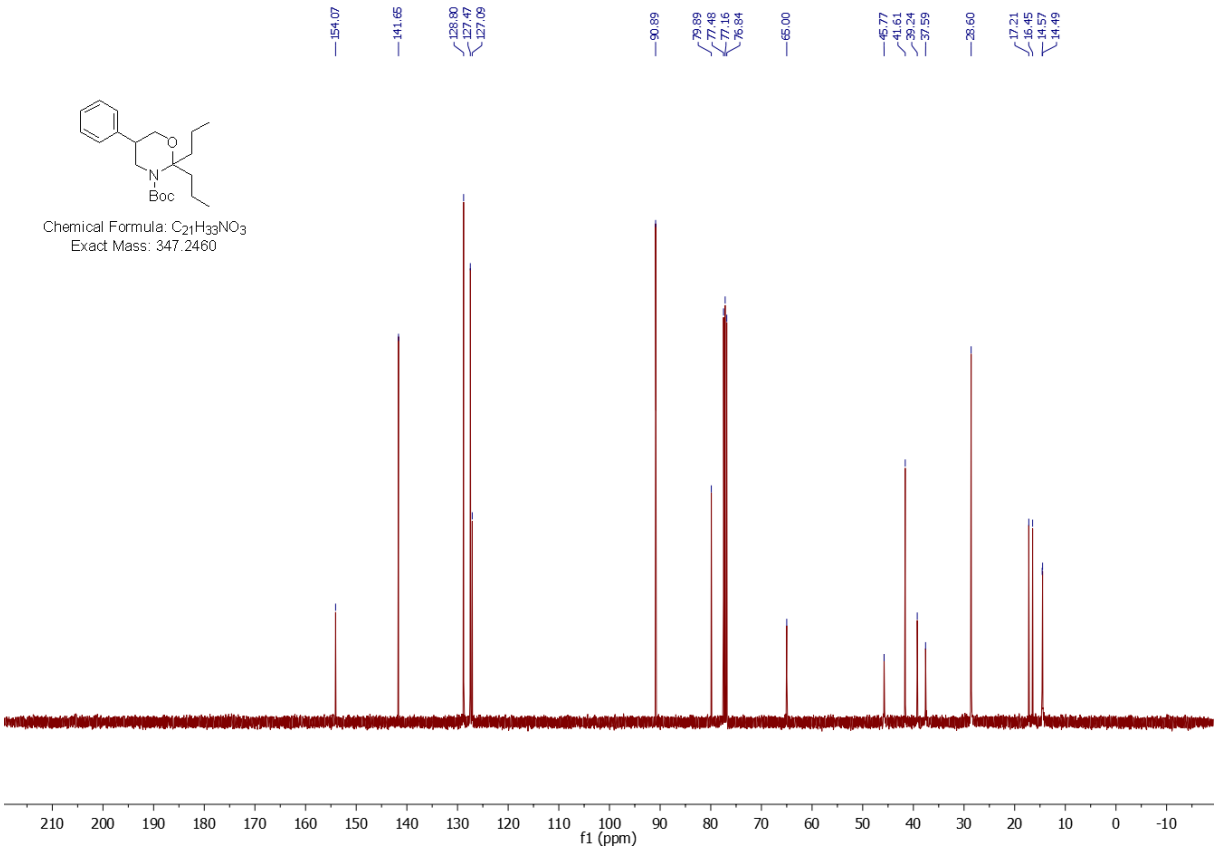
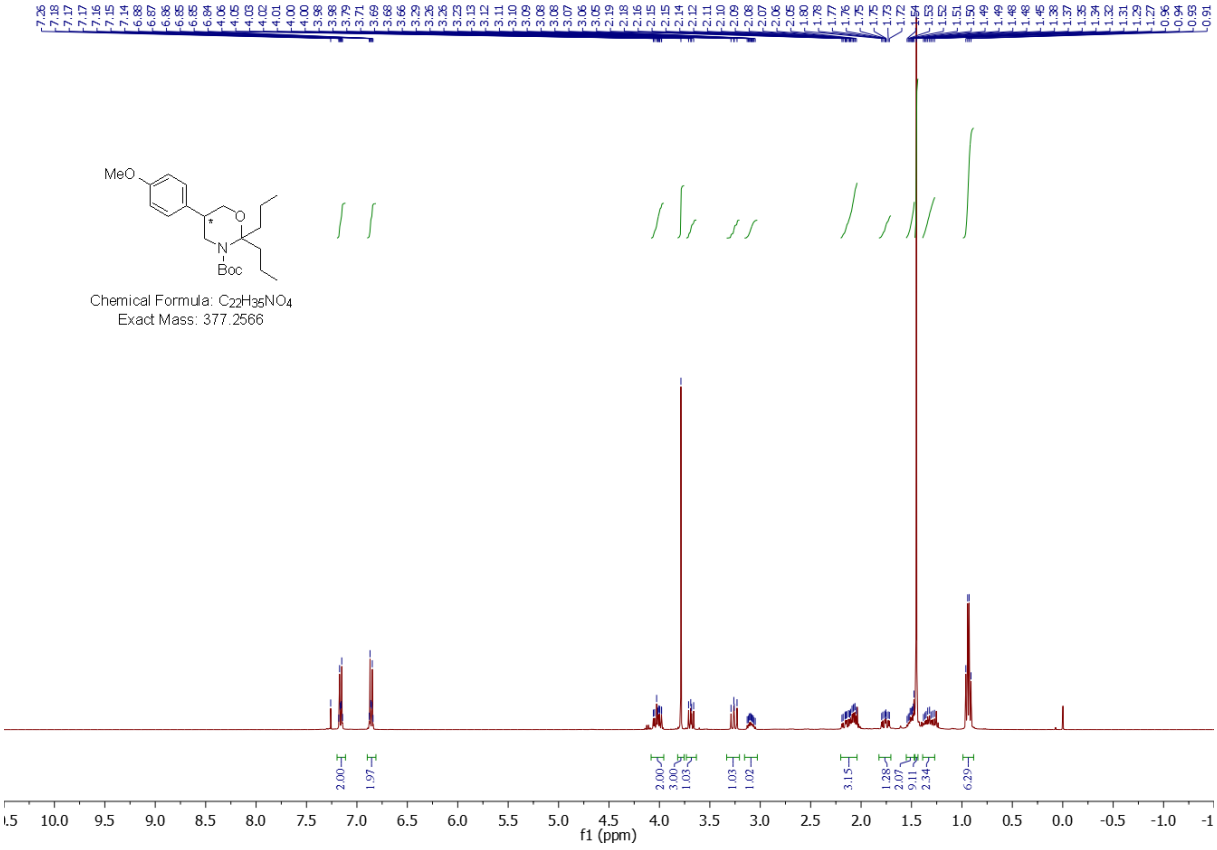
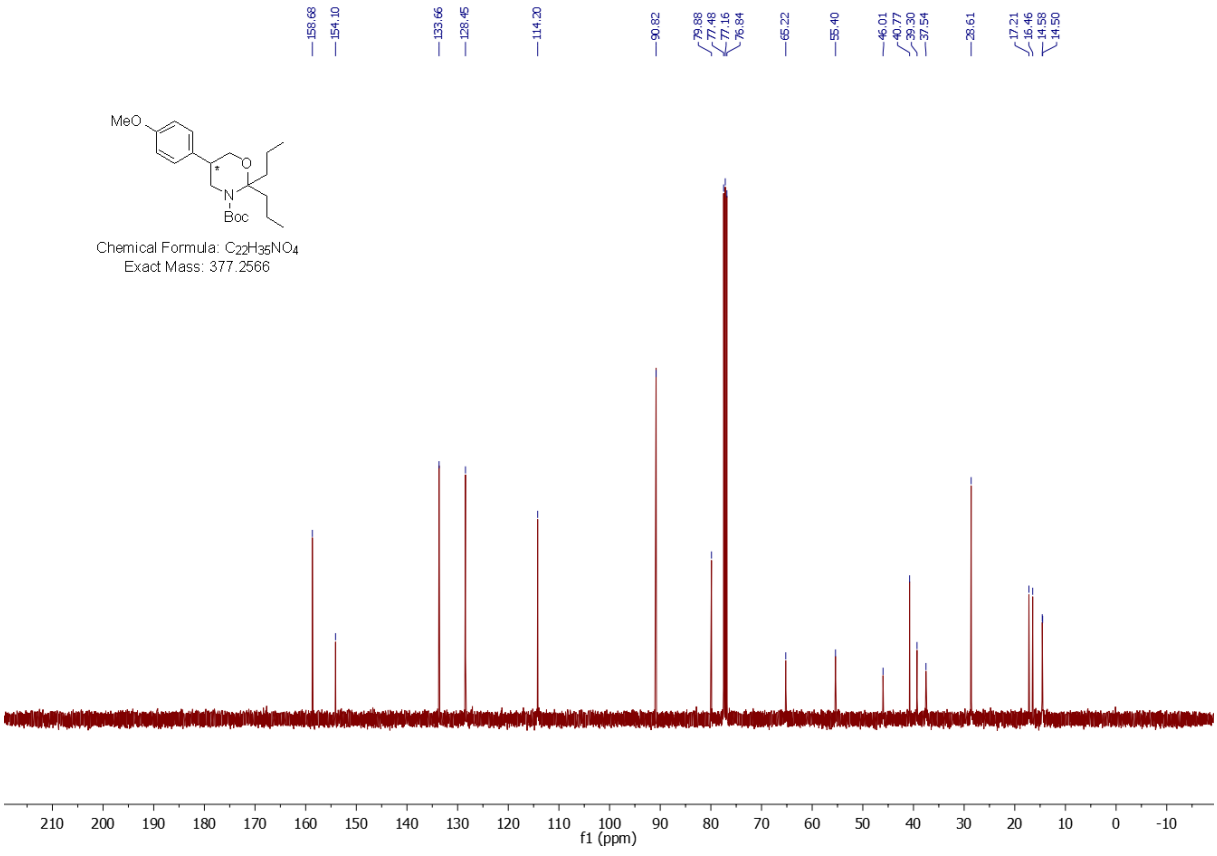
Exact Mass: 271.2147
f1 (ppm)

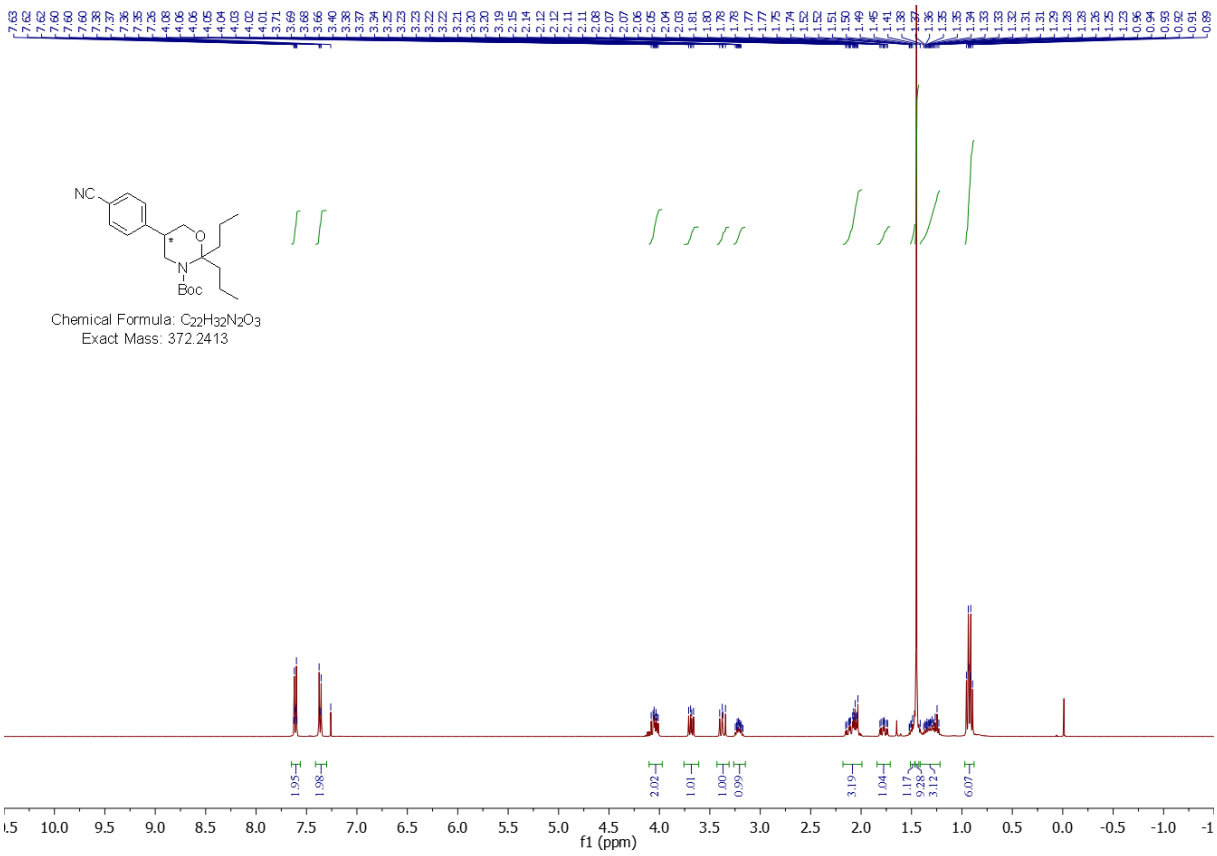

Boc
Chemical Formula: C15H29NO3
Exact Mass: 271.2147
f1 (ppm)

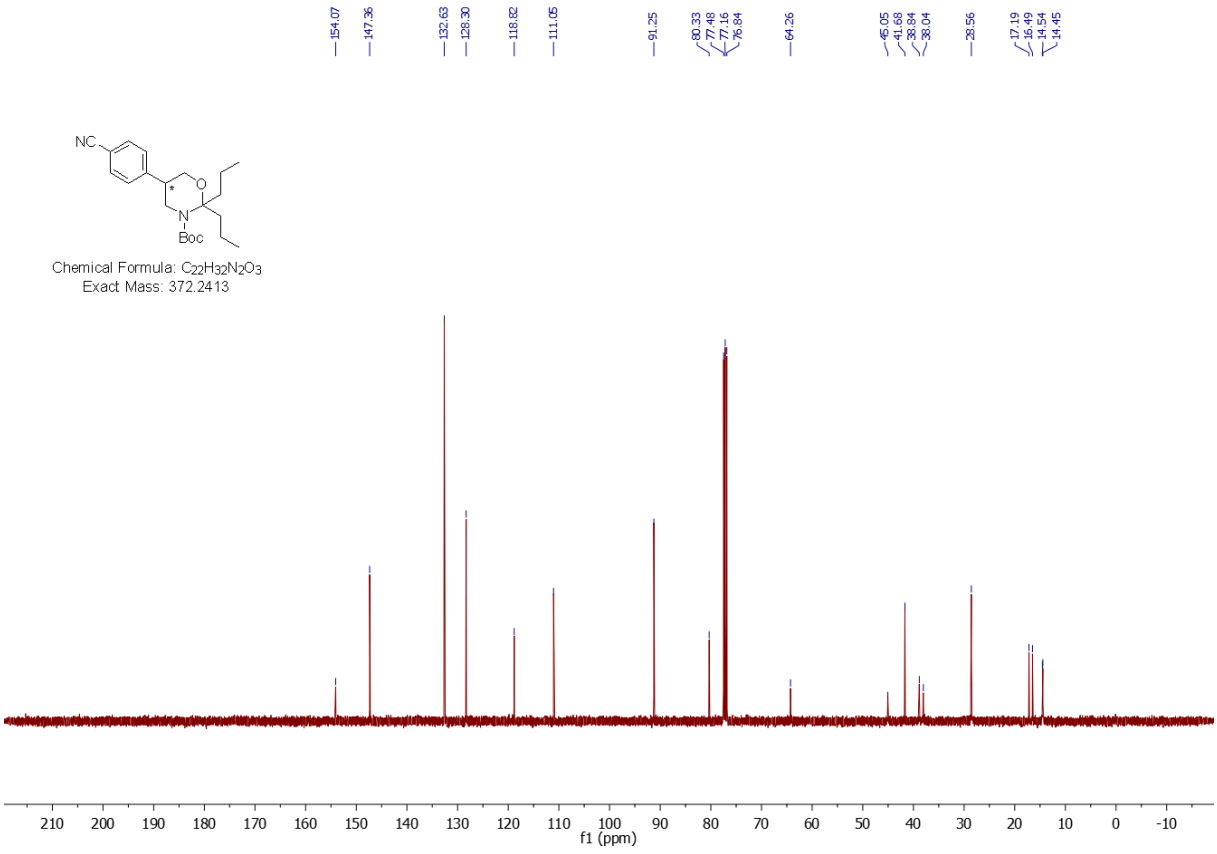

Boc
Chemical Formula: C21H33NO3
Exact Mass: 347.2460
f1 (ppm)

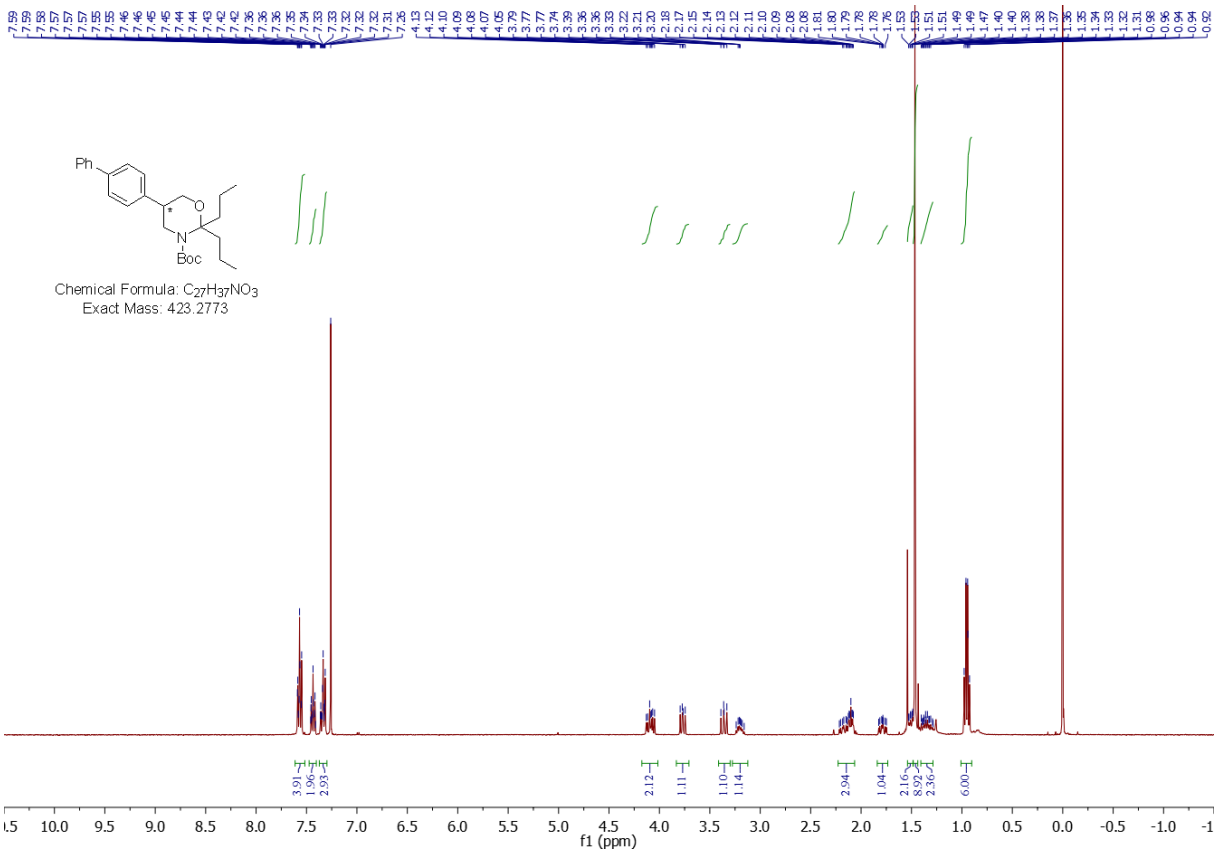

Boc
Chemical Formula: C21H33NO3
Exact Mass: 347.2460
f1 (ppm)

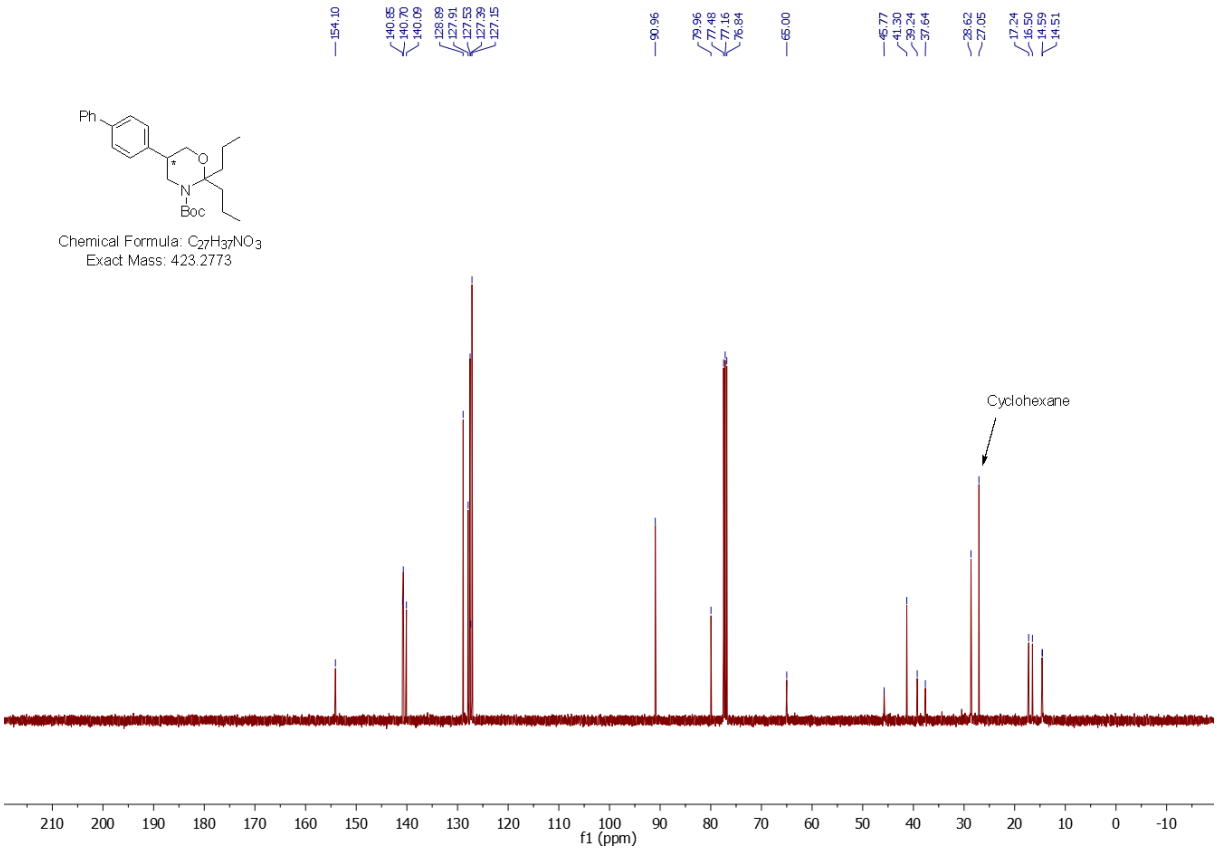

MeO
O
N
Boc
Chemical Formula: C22H35NO4
Exact Mass: 377.2566
f1 (ppm)

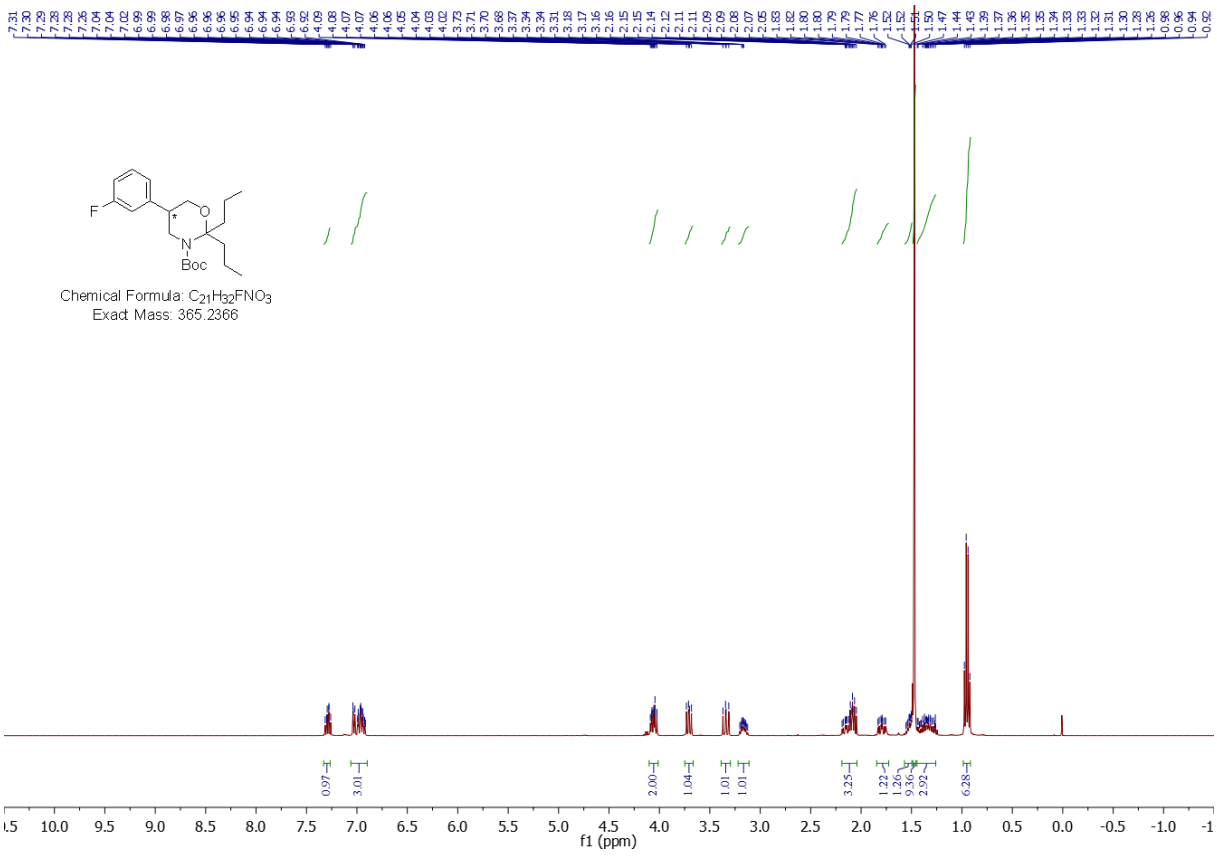

MeO
O
N
Boc
Chemical Formula: C22H35NO4
Exact Mass: 377.2566
f1 (ppm)

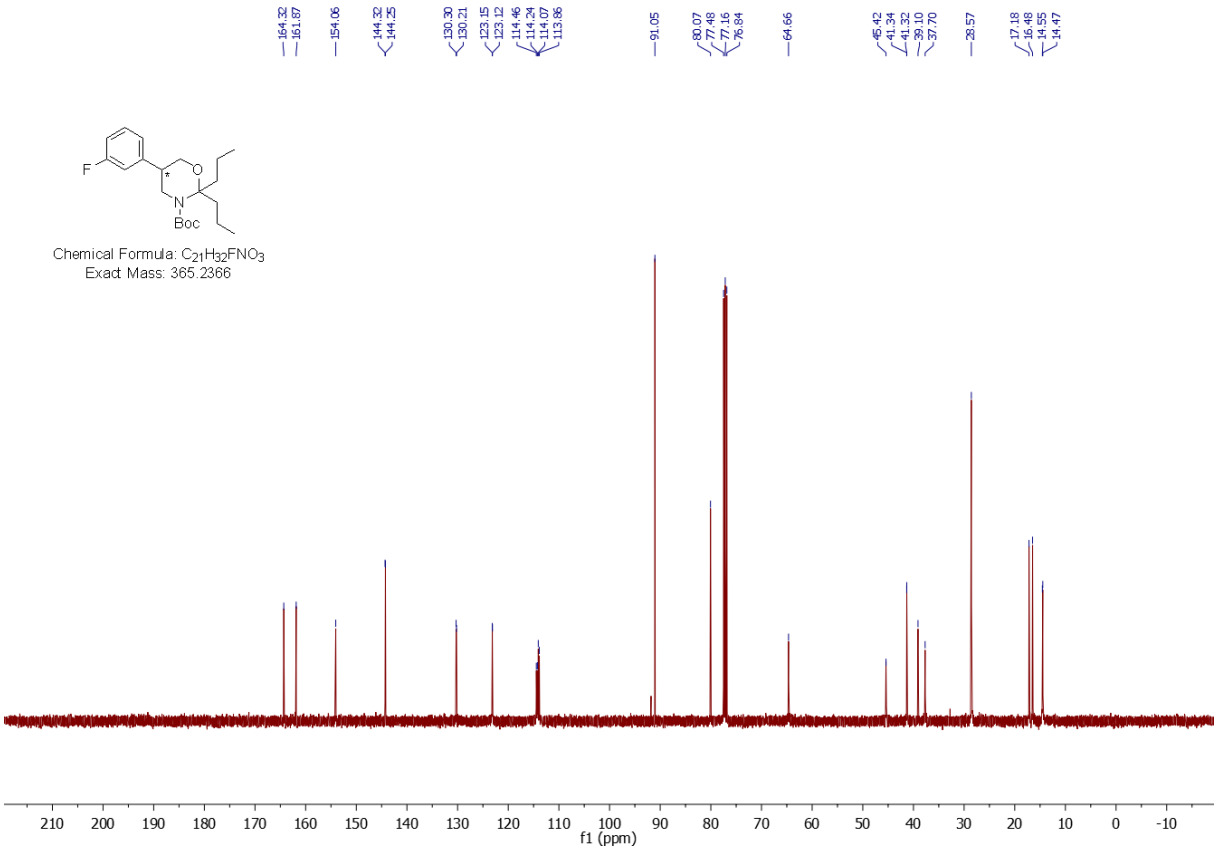

NC
O
N
Boc
Chemical Formula: C22H32N2O3
Exact Mass: 372.2413
1.95
1.98
2.02
1.01
1.00
0.99
3.19
1.04
1.17
9.28
3.12
6.07
f1 (ppm)

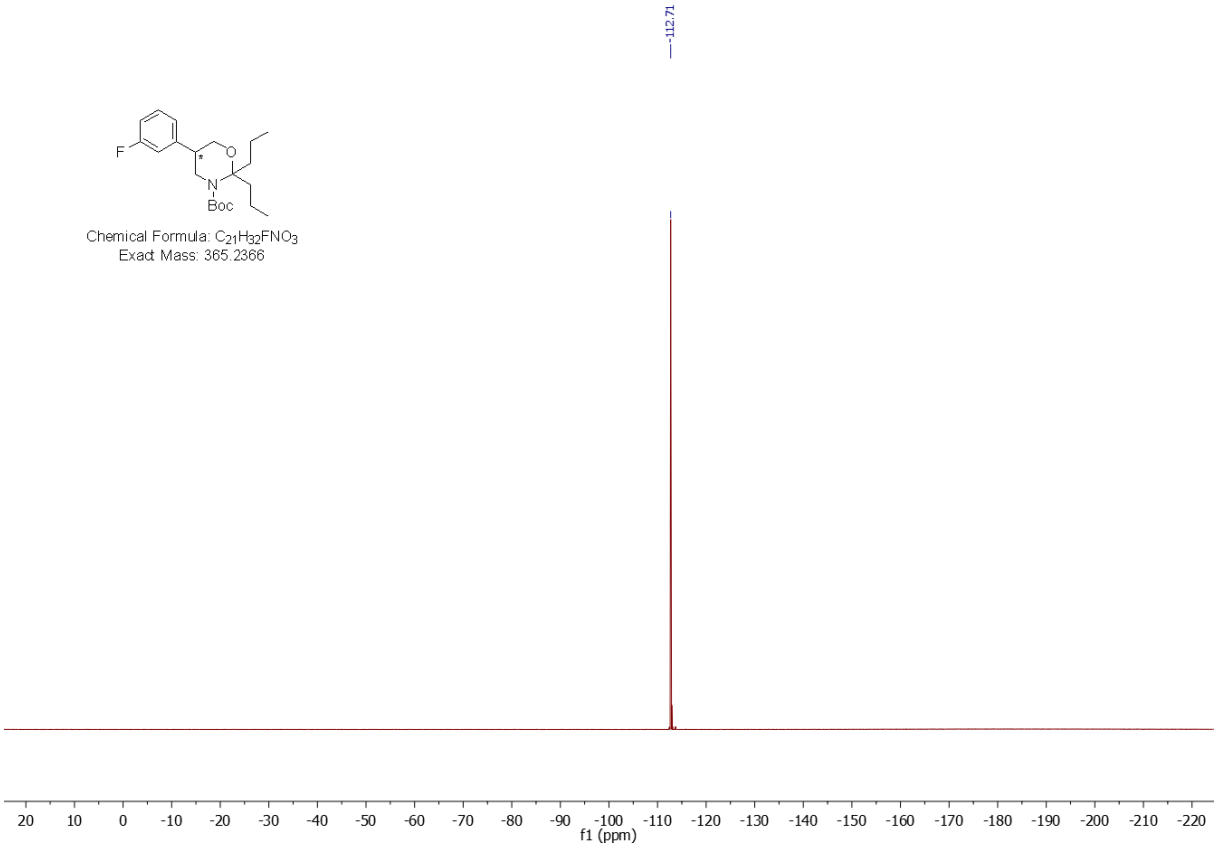

154.07
147.36
132.63
128.30
118.82
111.05
91.25
80.33
77.48
77.16
76.84
64.26
45.05
41.68
38.84
38.04
28.56
17.19
16.49
14.54
14.45
NC
O
N
Boc
Chemical Formula: C22H32N2O3
Exact Mass: 372.2413
f1 (ppm)

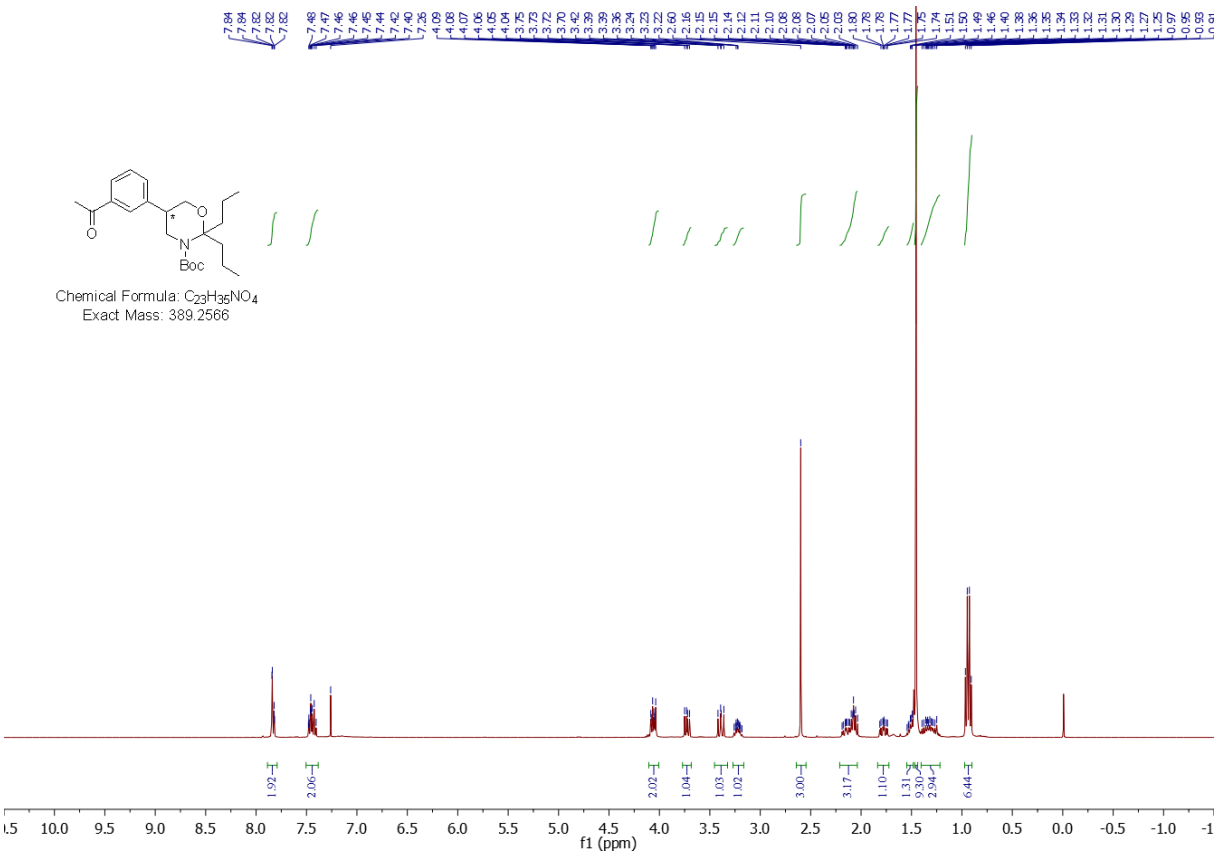

Ph
O
N
Boc
Chemical Formula: C27H37NO3
Exact Mass: 423.2773
f1 (ppm)

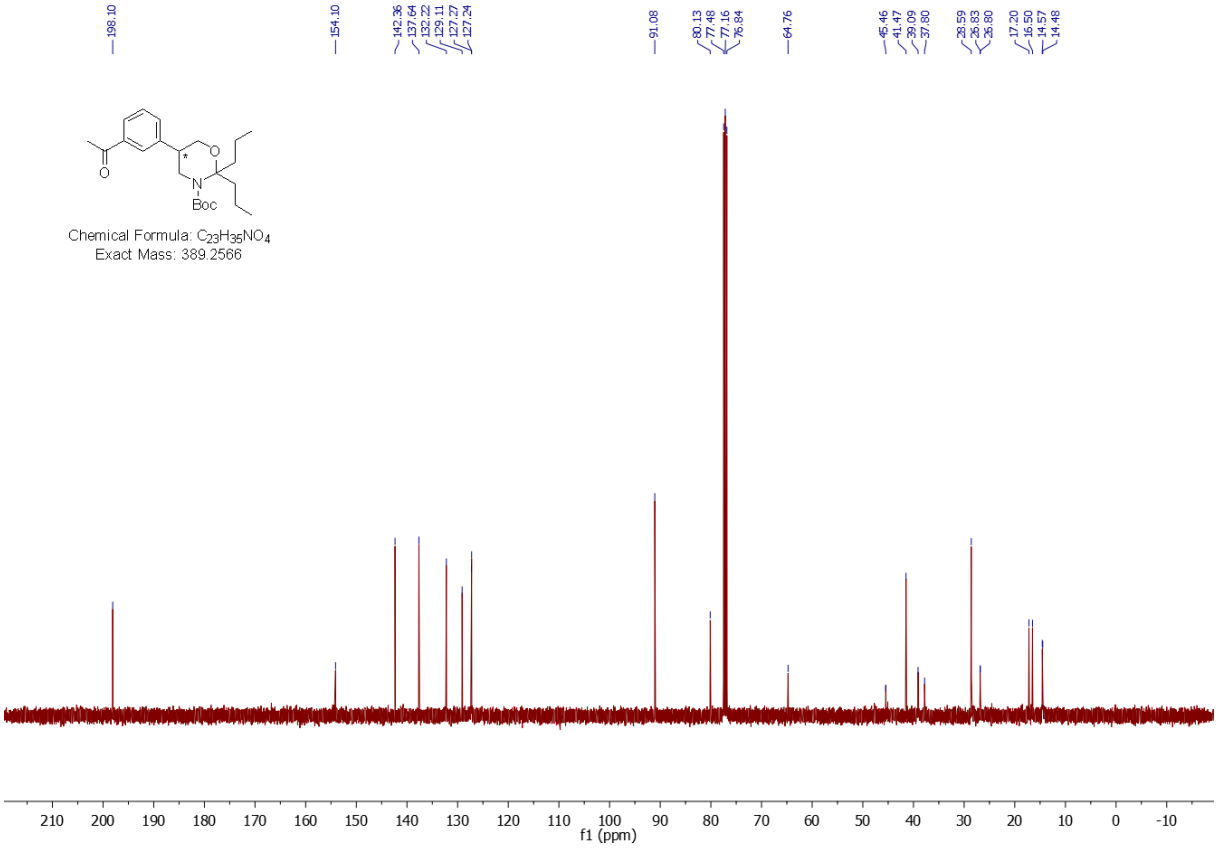

Ph
O
N
Boc
Chemical Formula: C27H37NO3
Exact Mass: 423.2773
Cyclohexane
f1 (ppm)

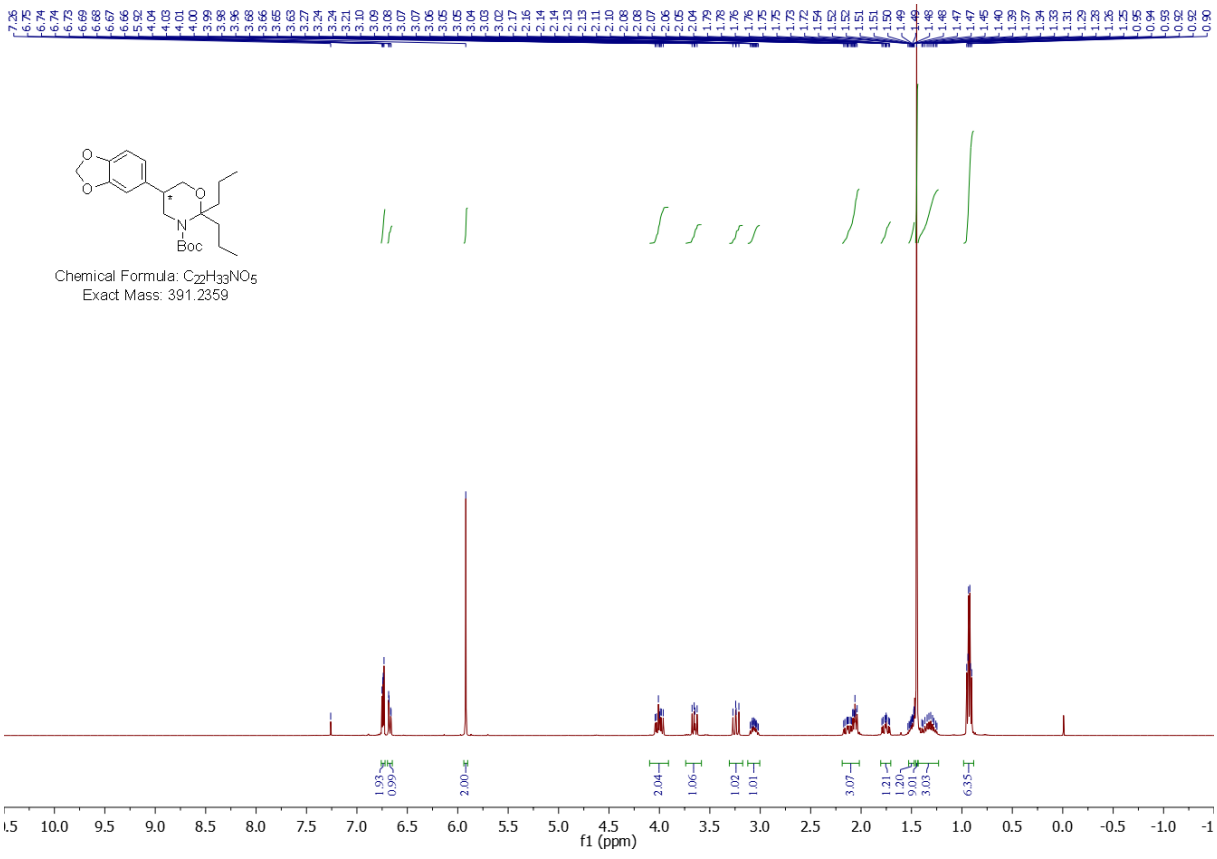

F
O
N
Boc
Chemical Formula: C21H32FNO3
Exact Mass: 365.2366
f1 (ppm)

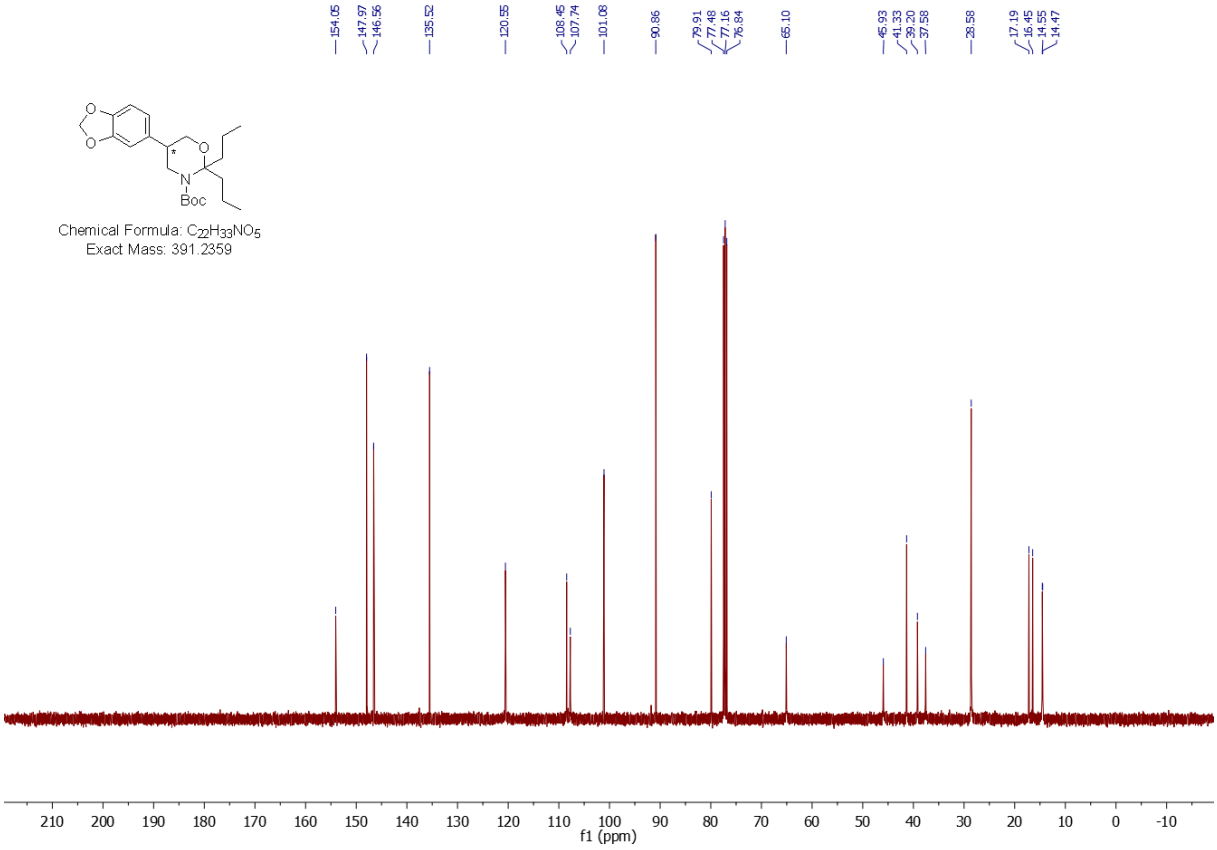

F
O
N
Boc
Chemical Formula: C21H32FNO3
Exact Mass: 365.2366
f1 (ppm)

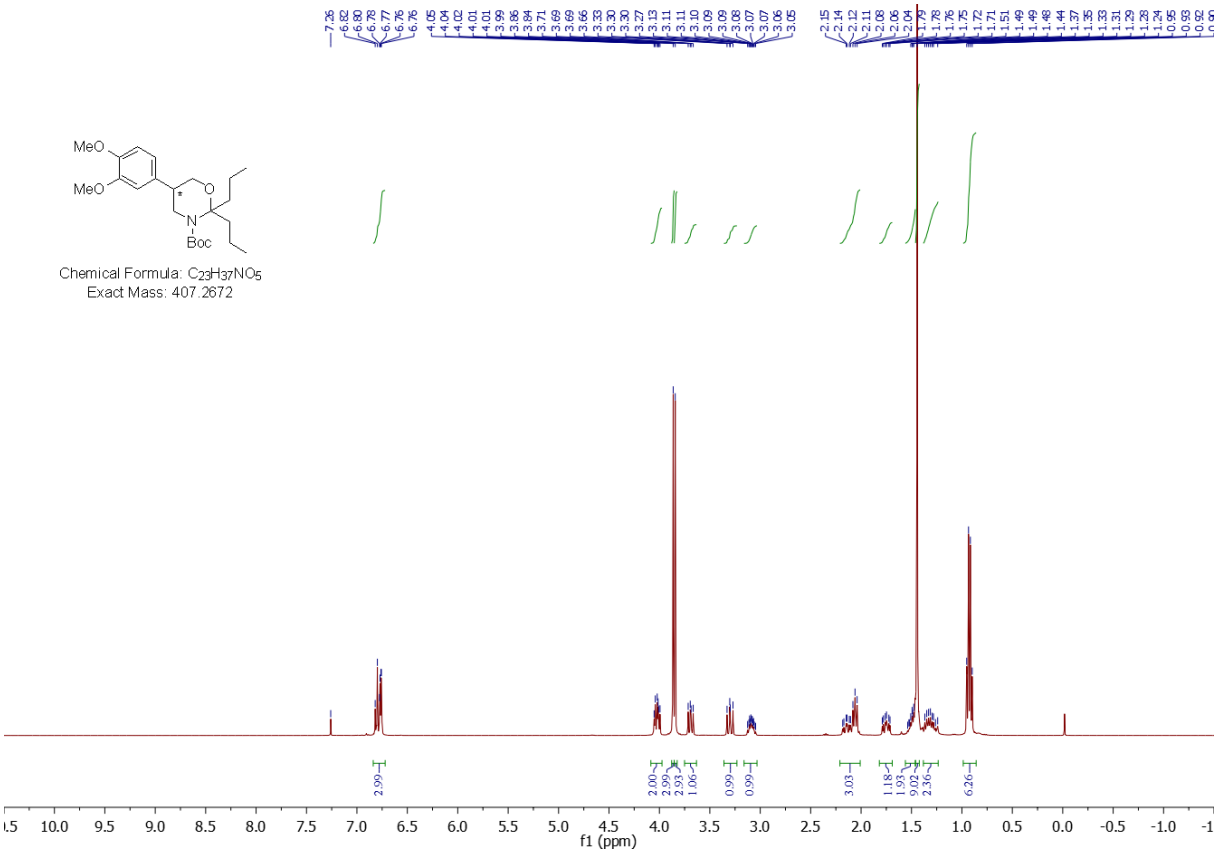

-112.71
F
O
N
Boc
Chemical Formula: C21H32FNO3
Exact Mass: 365.2366
f1 (ppm)

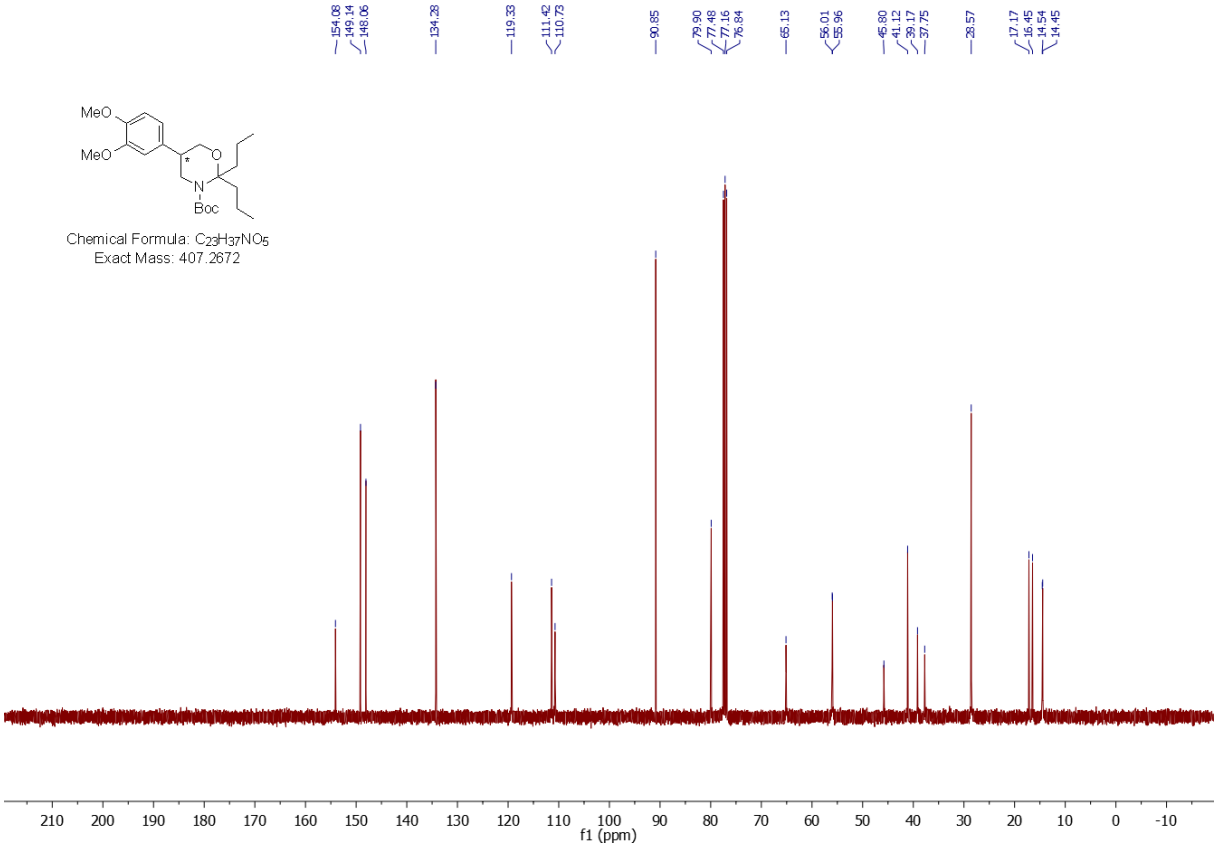

O
N
Boc
Chemical Formula: C23H35NO4
Exact Mass: 389.2566
1.92
2.06
2.02
1.04
1.03
1.02
3.00
3.17
1.10
1.31
9.30
2.94
6.44
f1 (ppm)

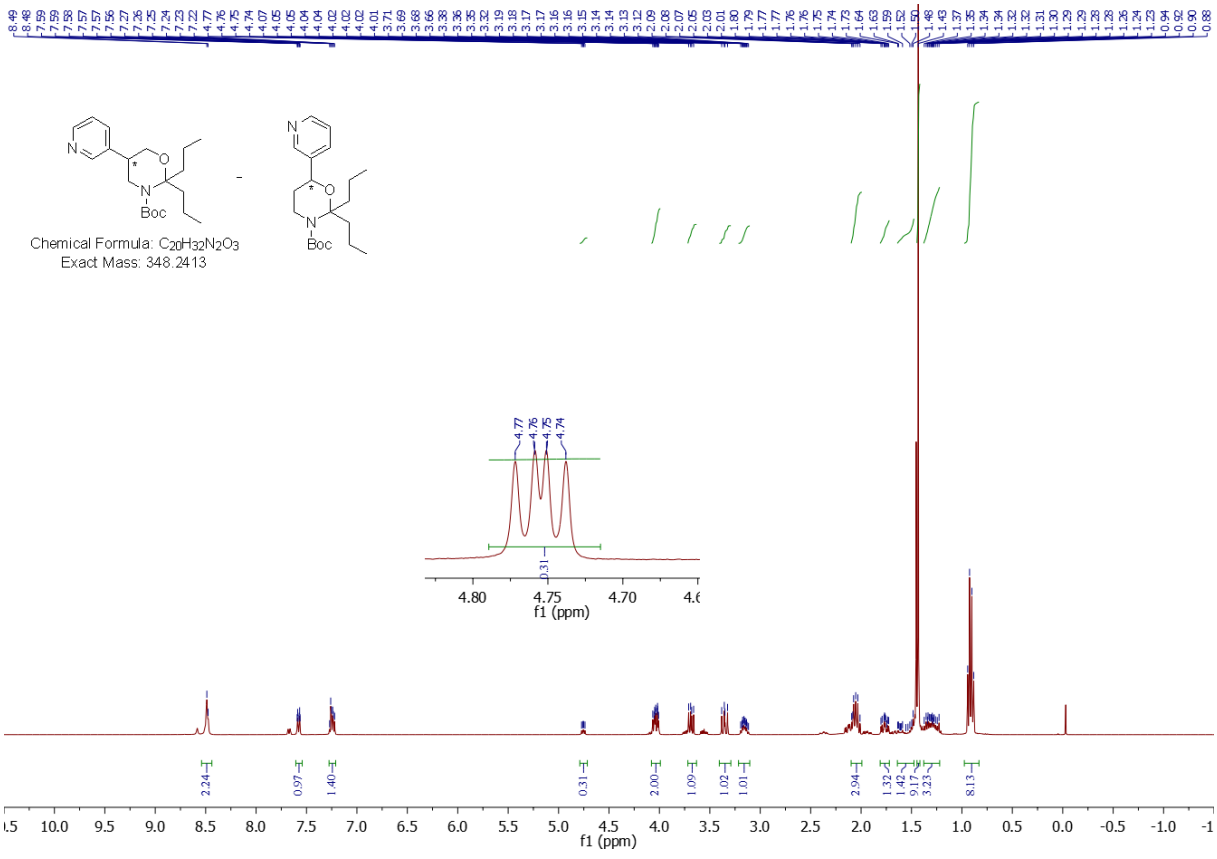

198.10
154.10
142.36
137.64
132.22
129.11
127.27
127.24
91.08
80.13
77.48
77.16
76.84
64.76
45.46
41.47
39.09
37.80
28.59
26.83
26.80
17.20
16.50
14.57
14.48
Boc
Chemical Formula: C23H35NO4
Exact Mass: 389.2566
f1 (ppm)

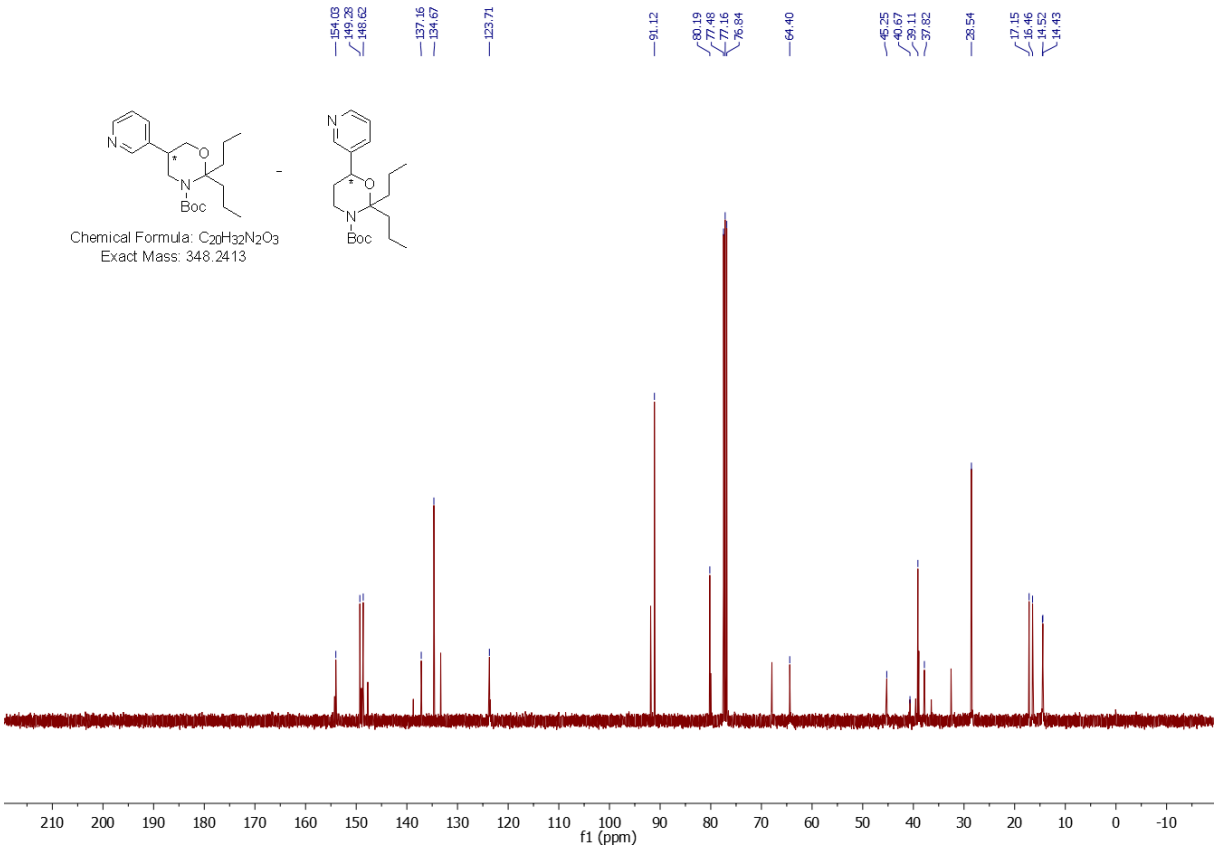

Boc
Chemical Formula: C22H33NO5
Exact Mass: 391.2359
f1 (ppm)

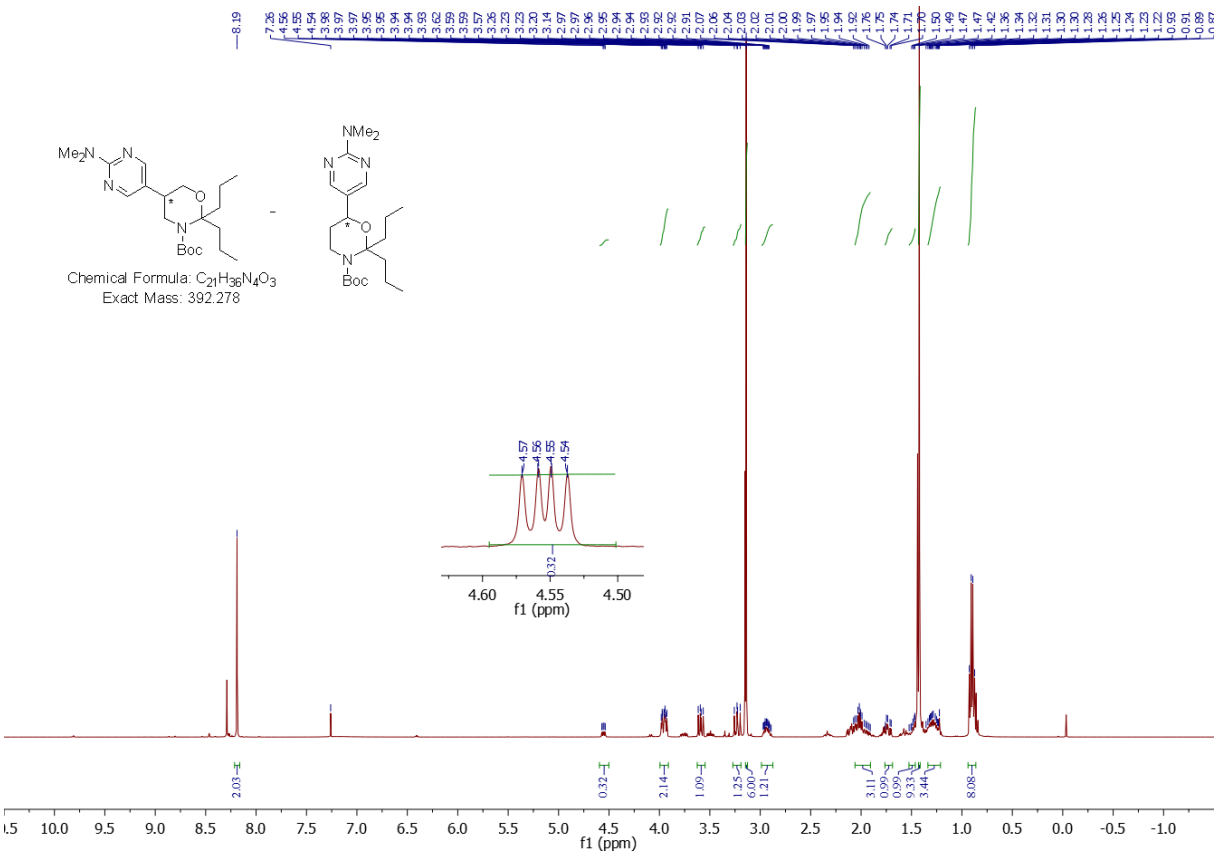

154.05
147.97
146.56
135.52
120.55
108.45
107.74
101.08
90.86
79.91
77.48
77.16
76.84
65.10
45.93
41.33
39.20
37.58
28.58
17.19
16.45
14.55
14.47
Boc
Chemical Formula: C22H33NO5
Exact Mass: 391.2359
f1 (ppm)

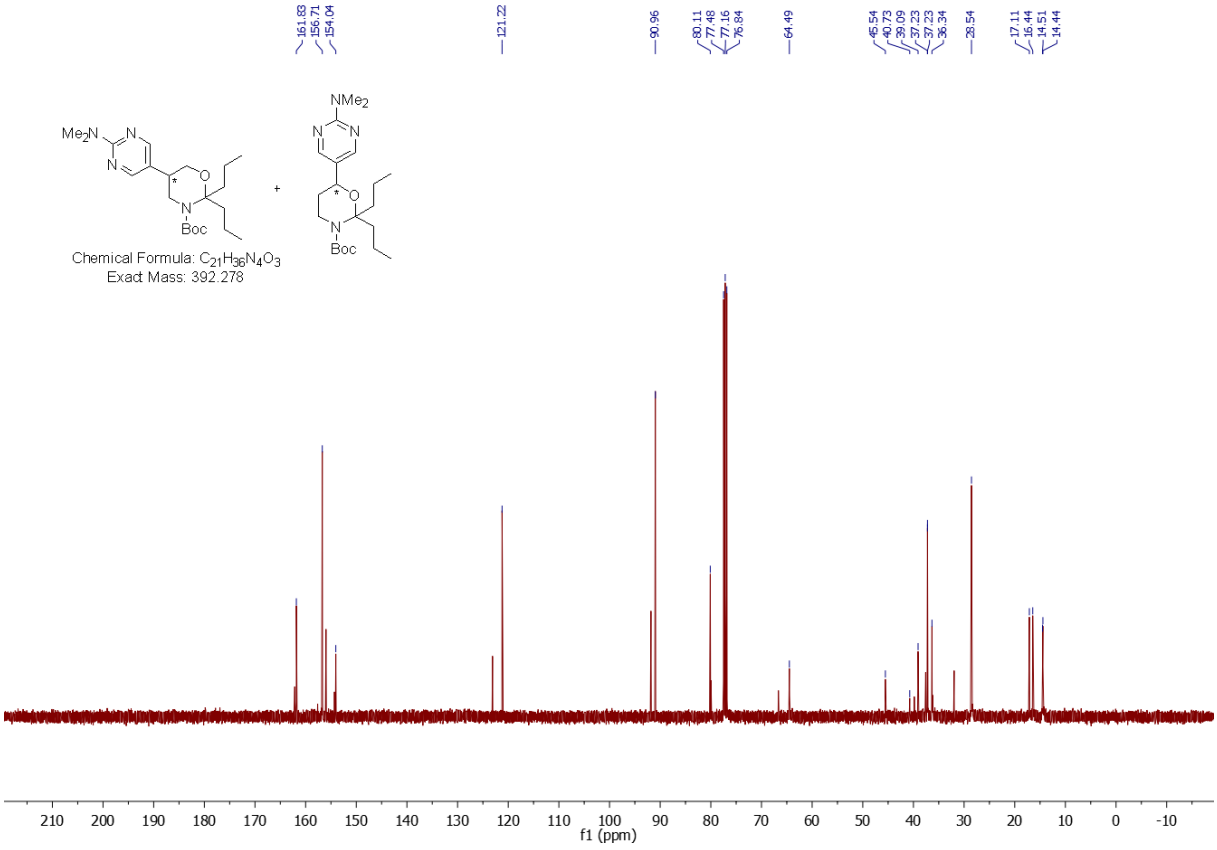

MeO
MeO
Boc
Chemical Formula: C23H37NO5
Exact Mass: 407.2672
f1 (ppm)

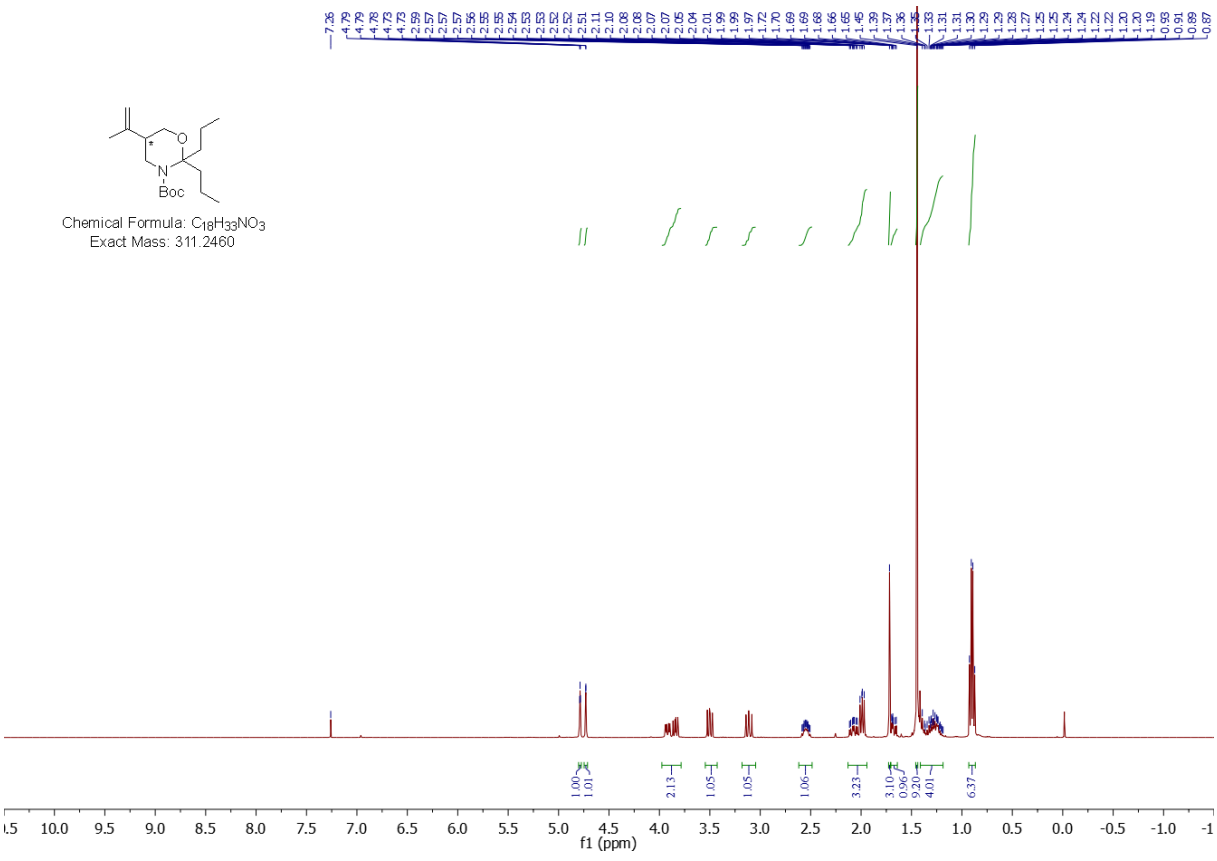

154.08
149.14
148.06
134.28
119.33
111.42
110.73
90.85
79.90
77.48
77.16
76.84
65.13
56.01
55.96
45.80
41.12
39.17
37.75
28.57
17.17
16.45
14.54
14.45
MeO
MeO
O
N
Boc
Chemical Formula: C23H37NO5
Exact Mass: 407.2672
f1 (ppm)

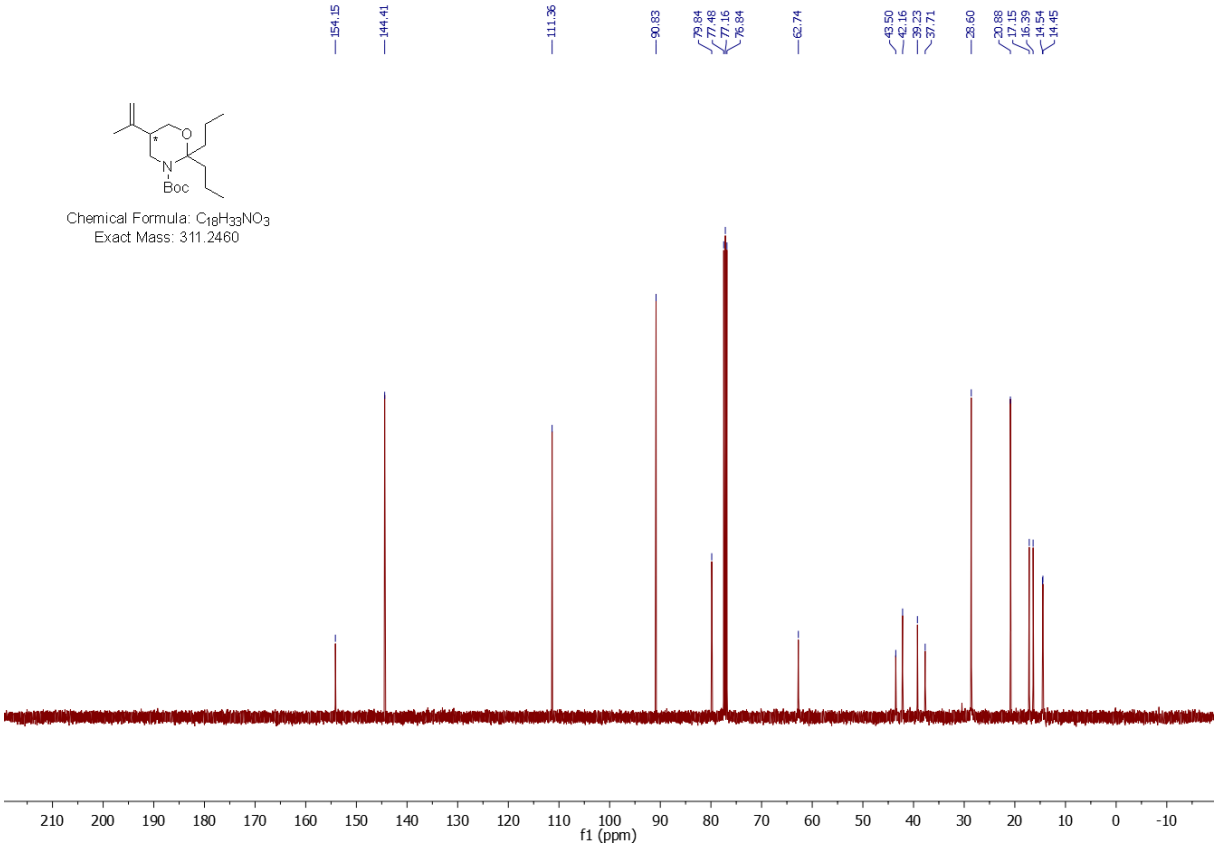

N
O
N
Boc
Chemical Formula: C20H32N2O3
Exact Mass: 348.2413
4.77
4.76
4.75
4.74
0.31
4.80
4.75
4.70
f1 (ppm)
2.24
0.97
1.40
0.31
2.00
1.09
1.02
1.01
2.94
1.32
1.42
9.17
3.23
8.13
f1 (ppm)

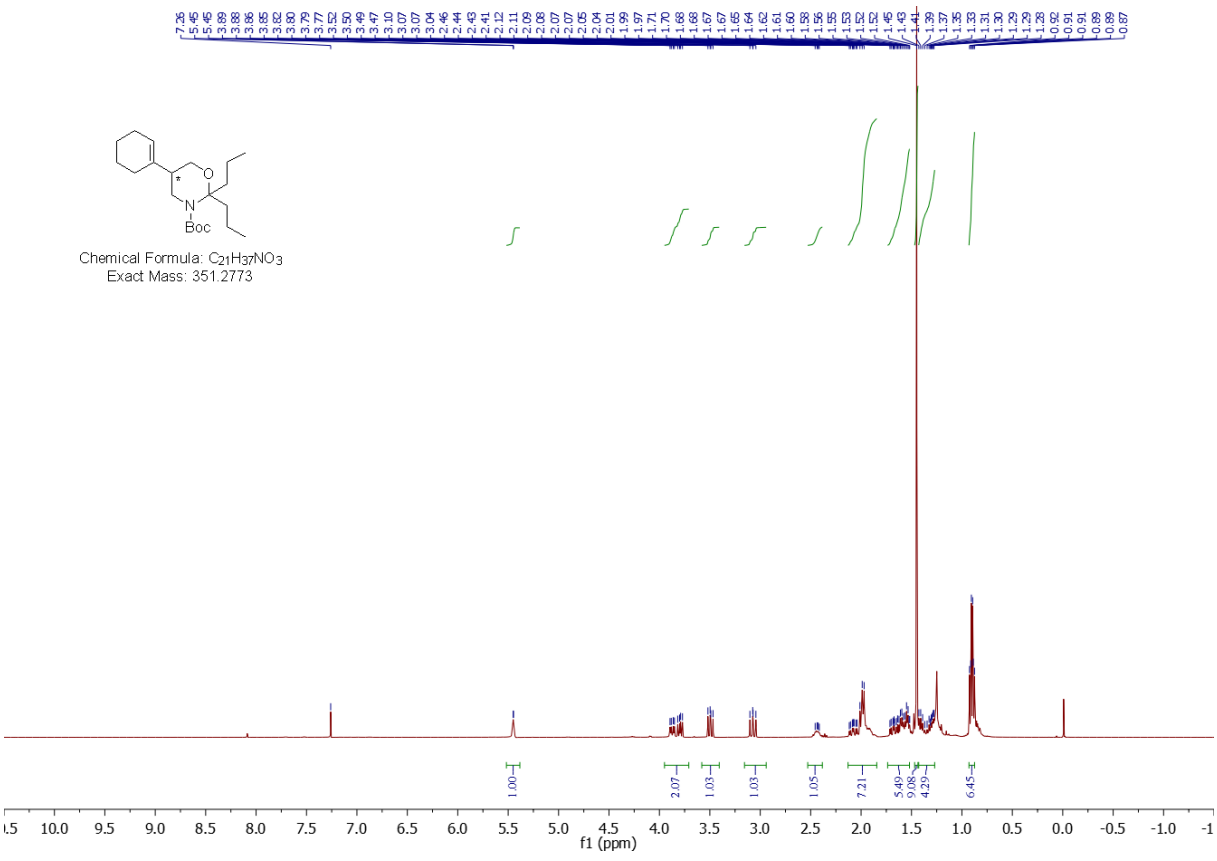

154.03
149.28
146.62
137.16
134.67
123.71
91.12
80.19
77.48
77.15
76.84
64.40
45.25
40.67
39.11
37.82
28.54
17.15
16.46
14.52
14.43
Boc
Chemical Formula: C20H32N2O3
Exact Mass: 348.2413
f1 (ppm)

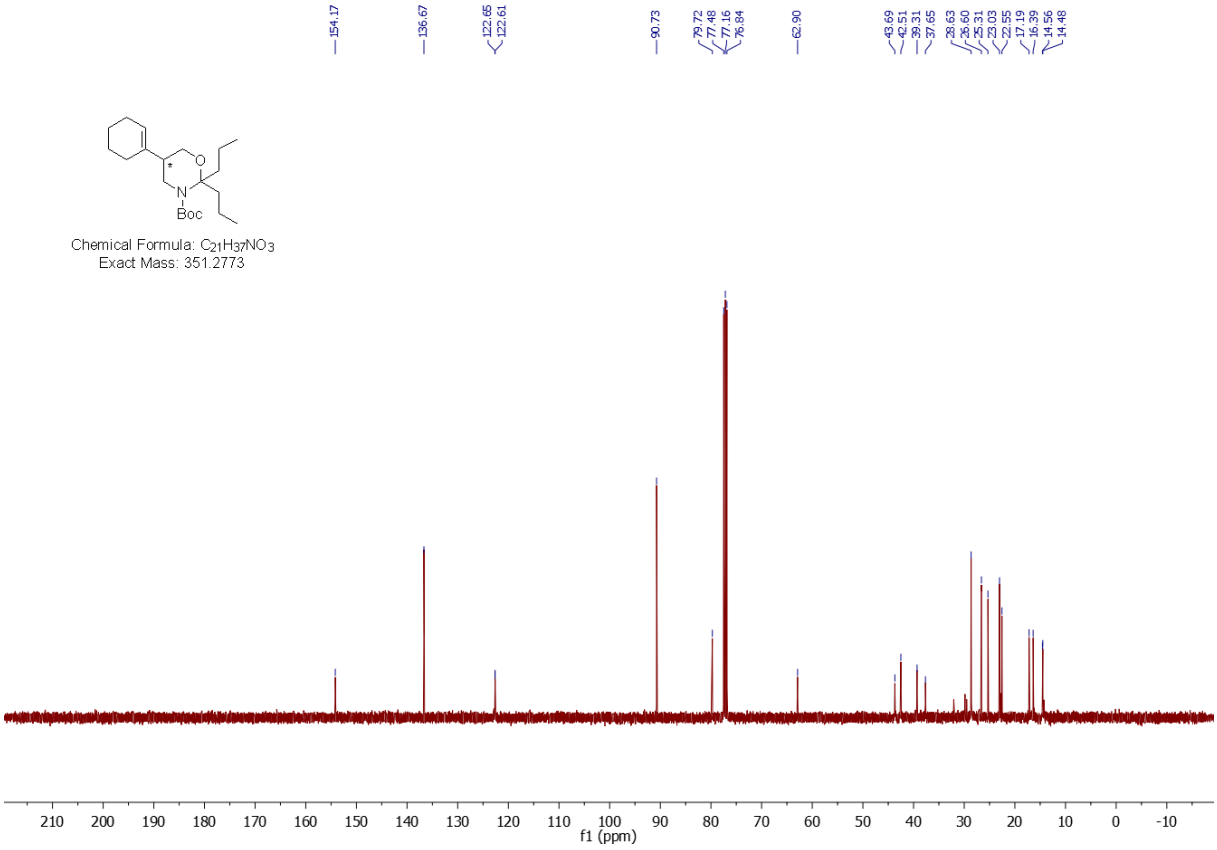

8.19
7.26
4.57
4.56
4.55
4.54
0.32
2.03
0.32
2.14
1.09
1.25
6.00
1.21
3.11
0.99
0.99
9.33
3.44
8.08
Me2N
NMe2
Boc
Chemical Formula: C21H36N4O3
Exact Mass: 392.278
f1 (ppm)

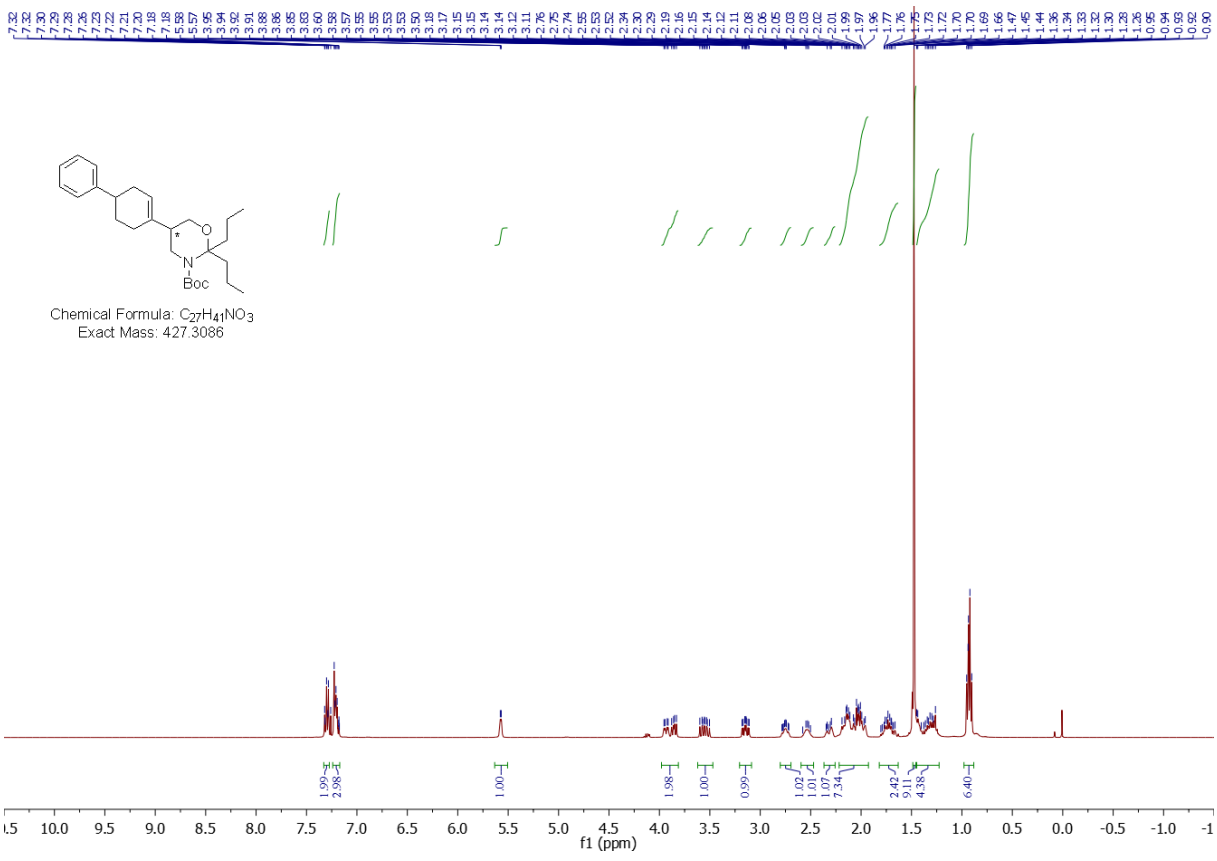

161.83
156.71
154.04
121.22
90.96
80.11
77.48
77.16
76.84
64.49
45.54
40.73
39.09
37.23
37.23
36.34
28.54
17.11
16.44
14.51
14.44
Me2N
NMe2
Boc
Chemical Formula: C21H36N4O3
Exact Mass: 392.278
f1 (ppm)

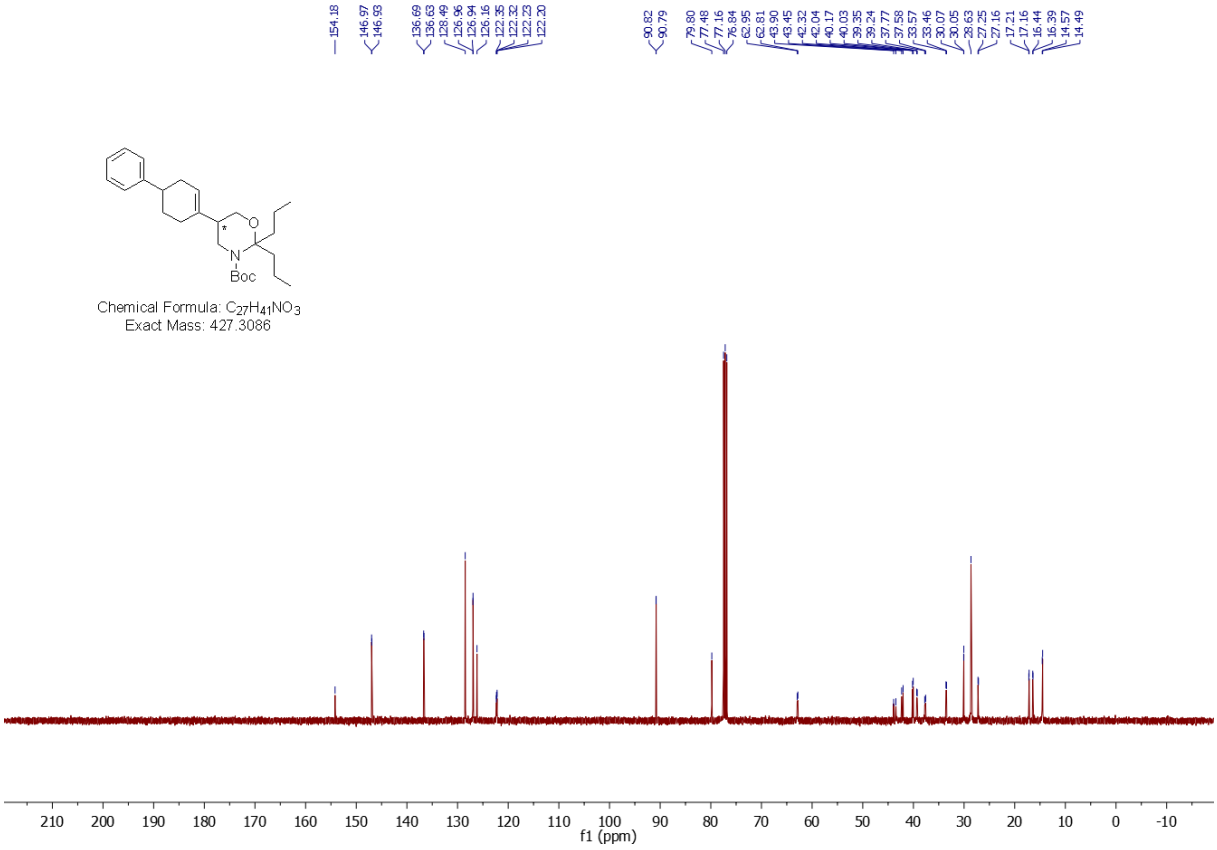

Boc
Chemical Formula: C18H33NO3
Exact Mass: 311.2460
1.00
1.01
2.13
1.05
1.05
1.06
3.23
3.10
0.96
9.20
4.01
6.37
f1 (ppm)

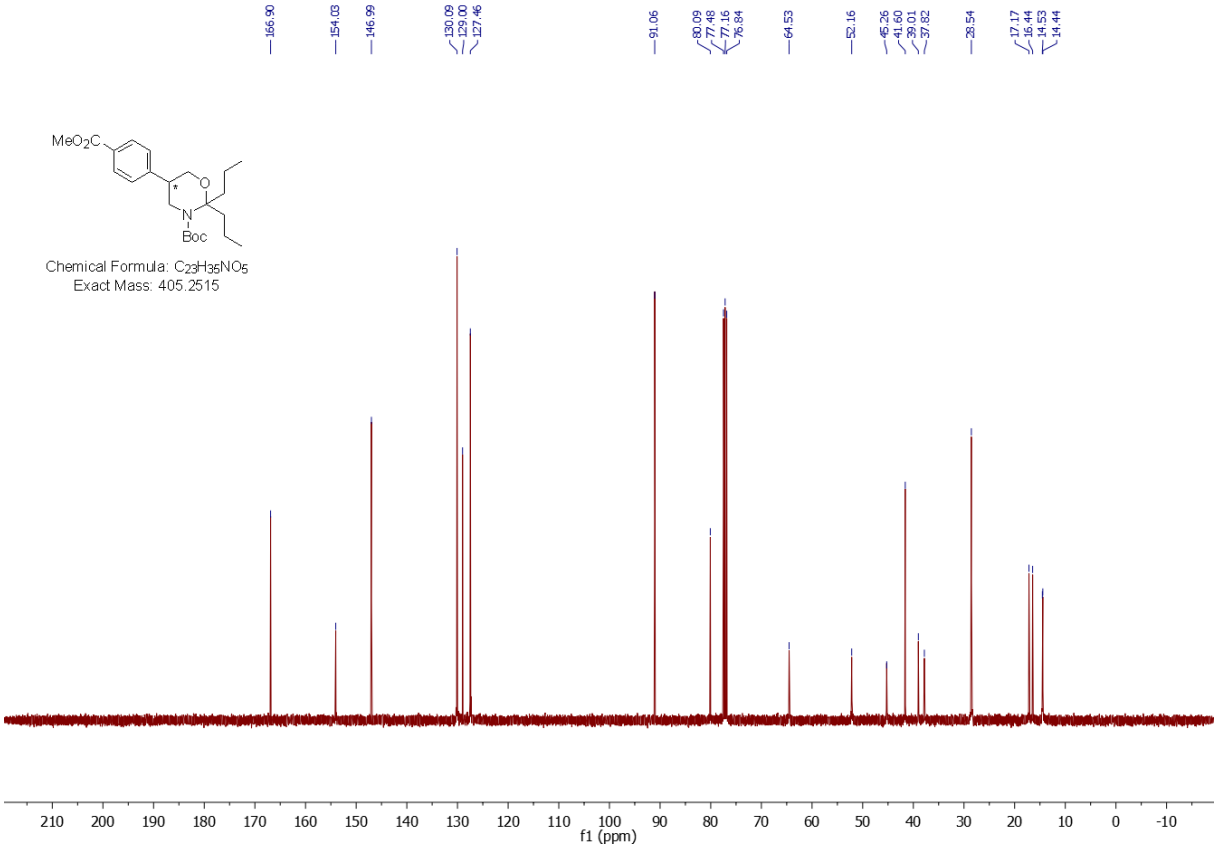

154.15
144.41
111.36
90.83
79.84
77.48
77.16
76.84
62.74
43.50
42.16
39.23
37.71
28.60
20.88
17.15
16.39
14.54
14.45
Boc
Chemical Formula: C18H33NO3
Exact Mass: 311.2460
f1 (ppm)

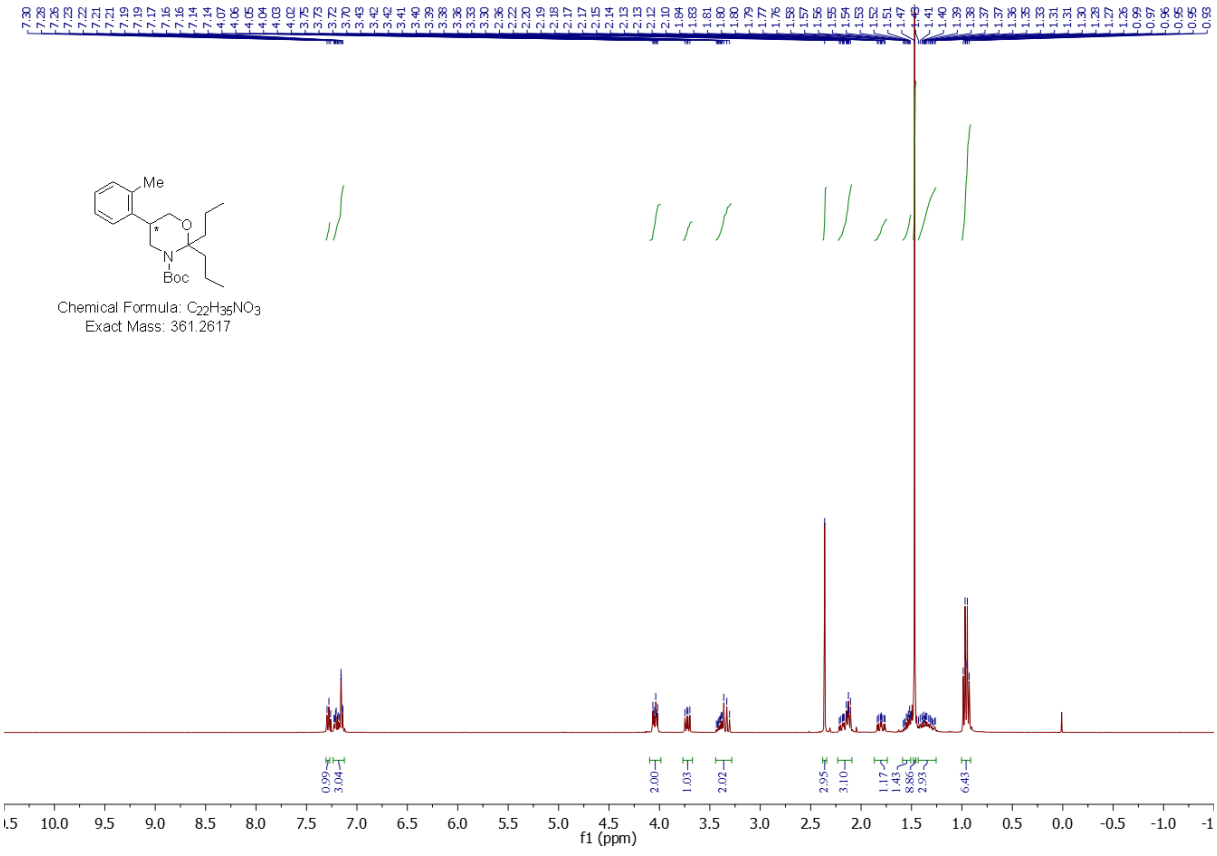

Boc
Chemical Formula: C21H37NO3
Exact Mass: 351.2773
1.00
2.07
1.03
1.03
1.05
7.21
5.49
9.08
4.29
6.45
f1 (ppm)

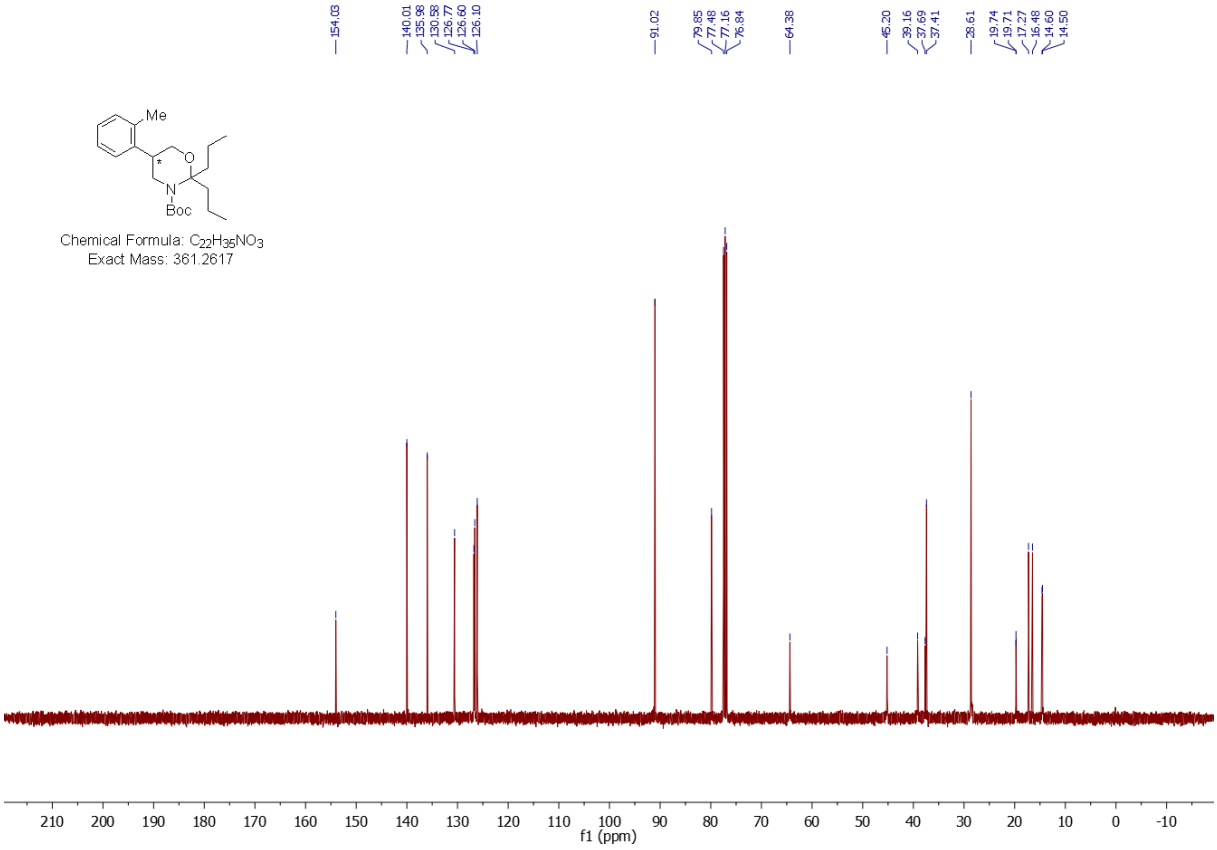

154.17
136.67
122.65
122.61
90.73
79.72
77.48
77.16
76.84
62.90
43.69
42.51
39.31
37.65
28.63
26.60
25.31
23.03
22.55
17.19
16.39
14.56
14.48
Boc
Chemical Formula: C21H37NO3
Exact Mass: 351.2773
f1 (ppm)

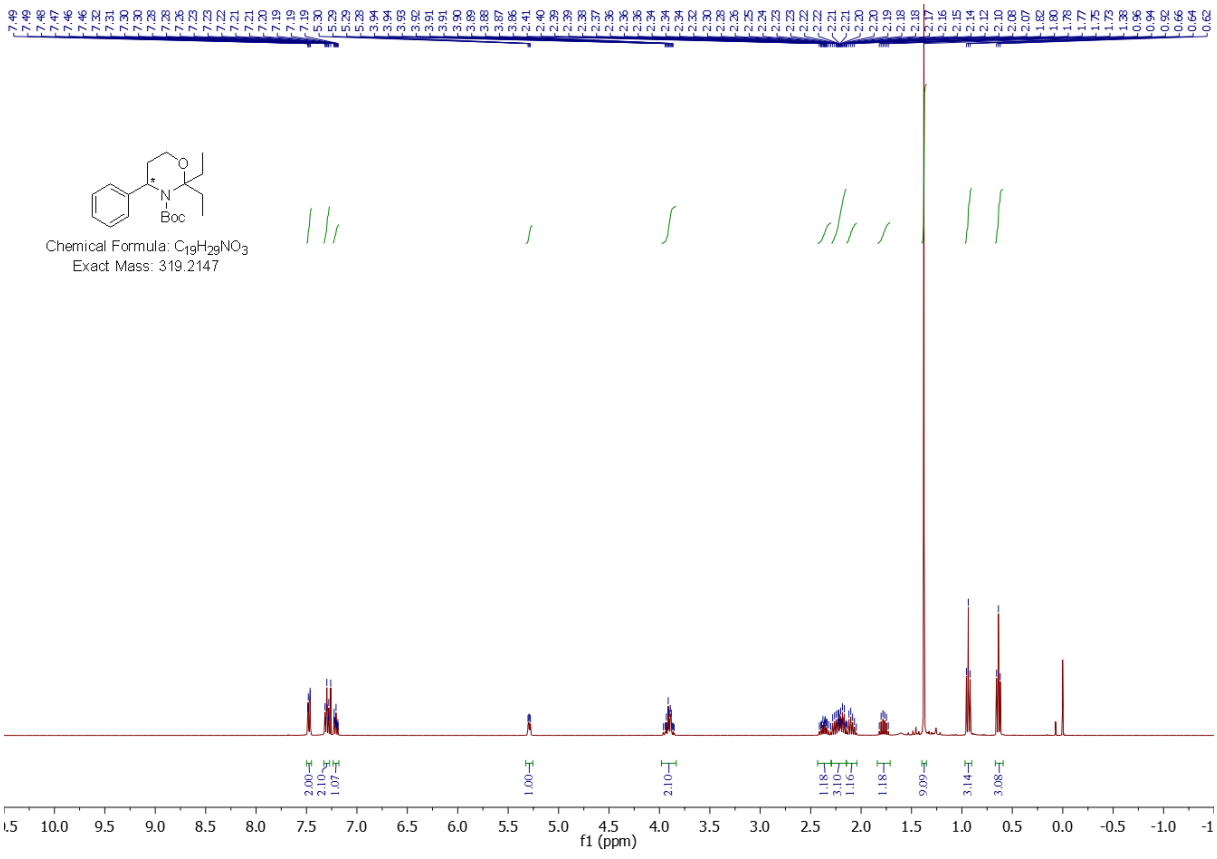

Boc
Chemical Formula: C27H41NO3
Exact Mass: 427.3086
1.99
2.98
1.00
1.98
1.00
0.99
1.02
1.01
1.07
7.34
2.42
9.11
4.38
6.40
f1 (ppm)

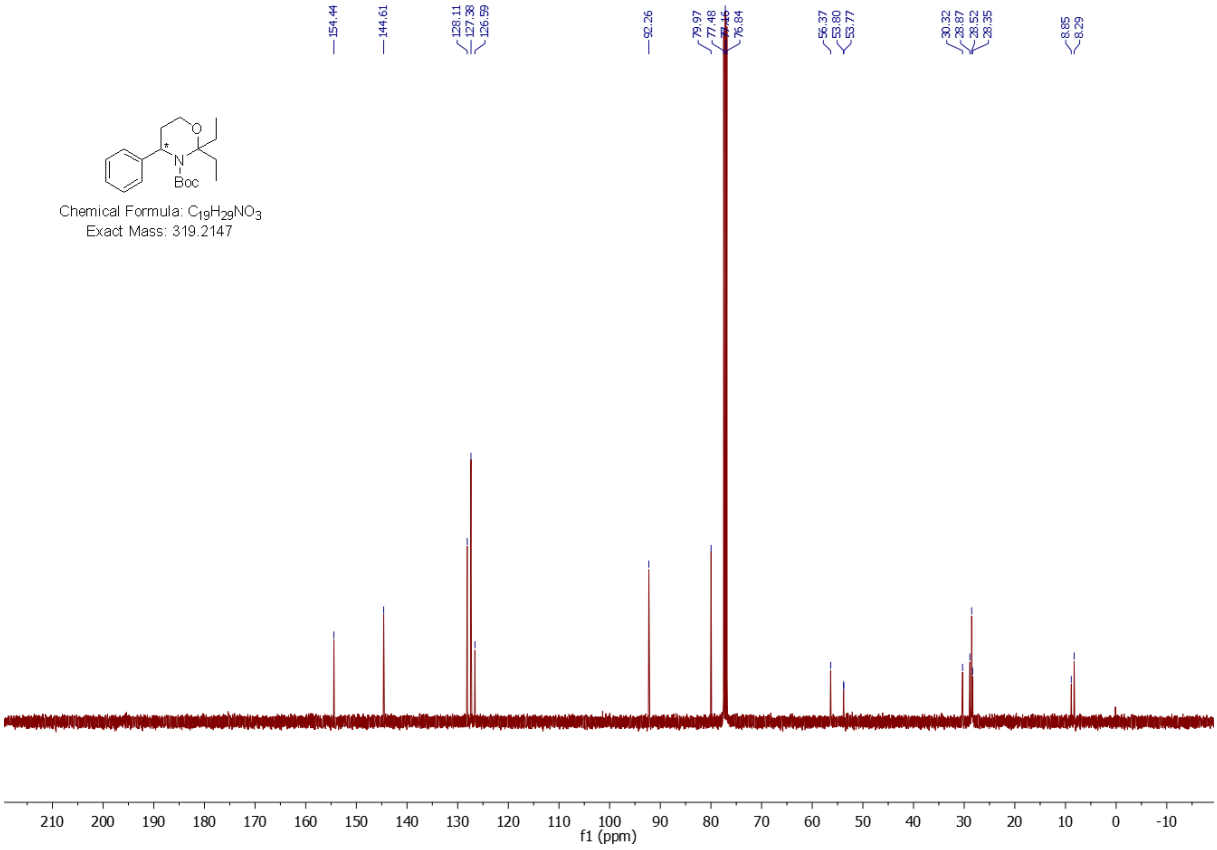

Boc
Chemical Formula: C27H41NO3
Exact Mass: 427.3086
f1 (ppm)
MeO2C
Boc
Chemical Formula: C23H35NO5
Exact Mass: 405.2515
f1 (ppm)

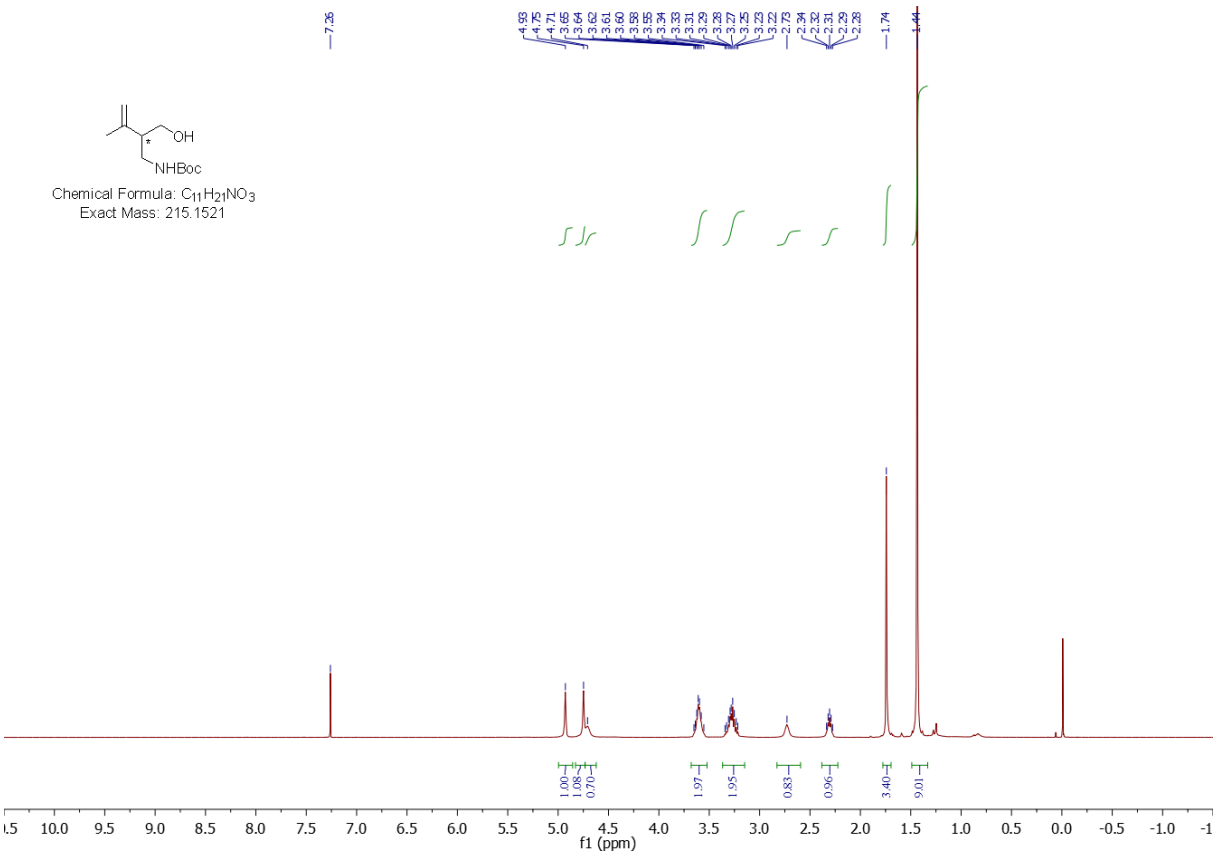

166.90
154.03
146.99
130.09
129.00
127.46
91.06
80.09
77.48
77.16
76.84
64.53
52.16
45.26
41.60
39.01
37.82
28.54
17.17
16.44
14.53
14.44
MeO2C
O
N
Boc
Chemical Formula: C23H35NO5
Exact Mass: 405.2515
f1 (ppm)

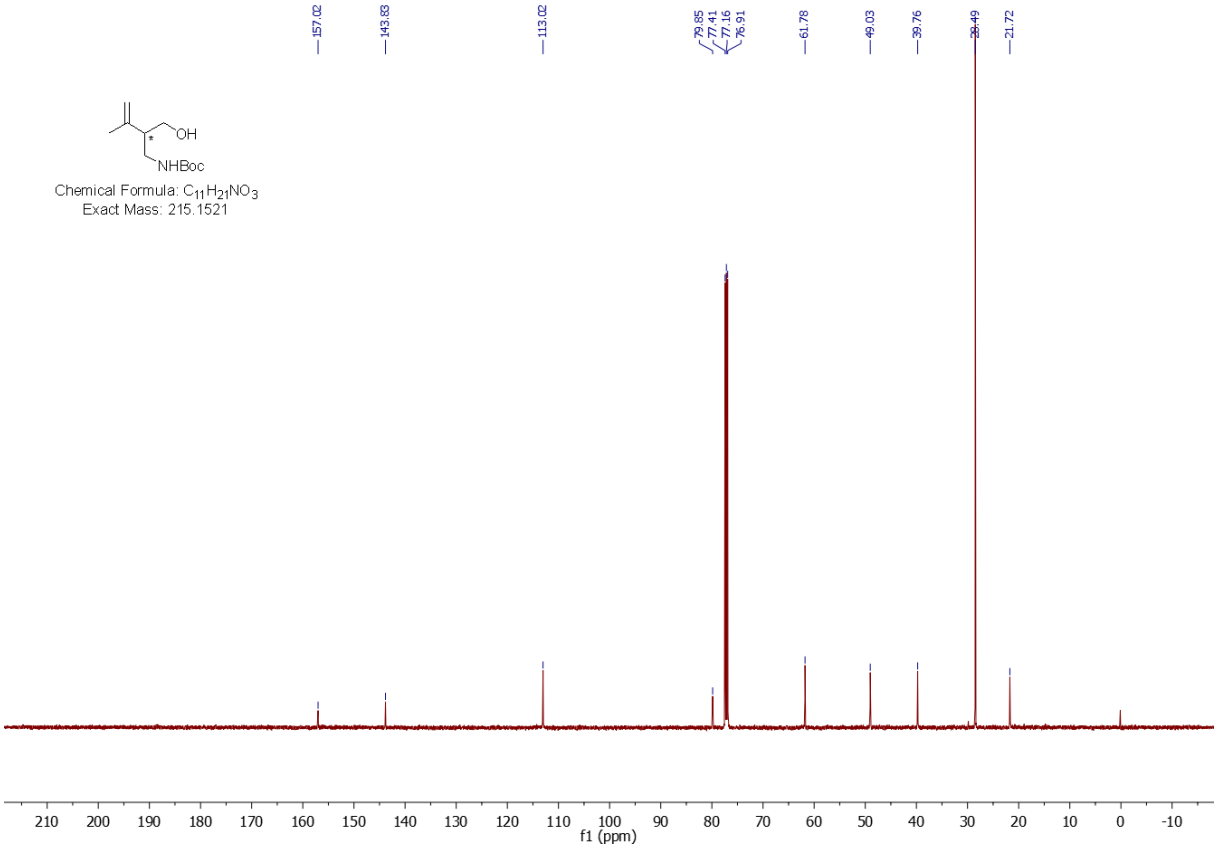

Me
O
N
Boc
Chemical Formula: C22H35NO3
Exact Mass: 361.2617
f1 (ppm)

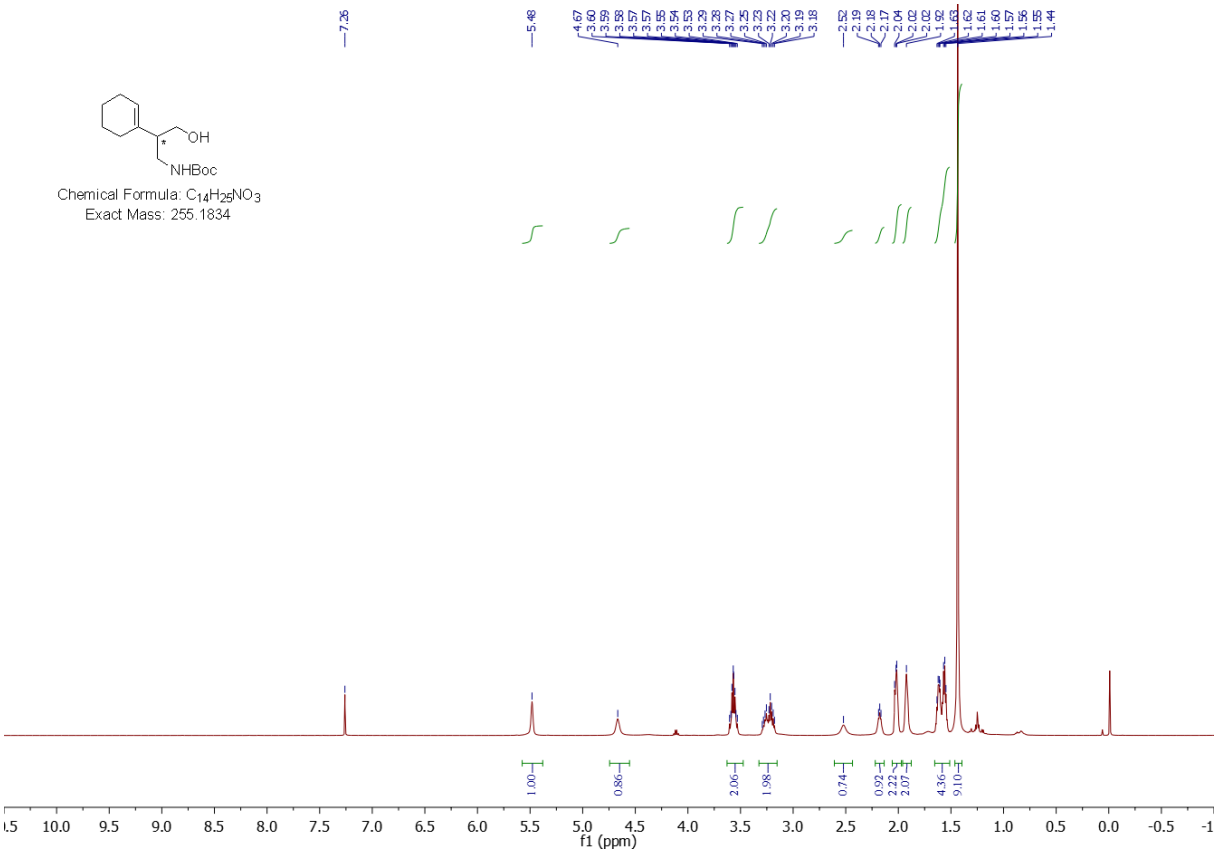

154.03
140.01
135.98
130.58
126.77
126.60
126.10
91.02
79.85
77.48
77.16
76.84
64.38
45.20
39.16
37.69
37.41
28.61
19.74
19.71
17.27
16.48
14.60
14.50
Me
O
N
Boc
Chemical Formula: C22H35NO3
Exact Mass: 361.2617
f1 (ppm)

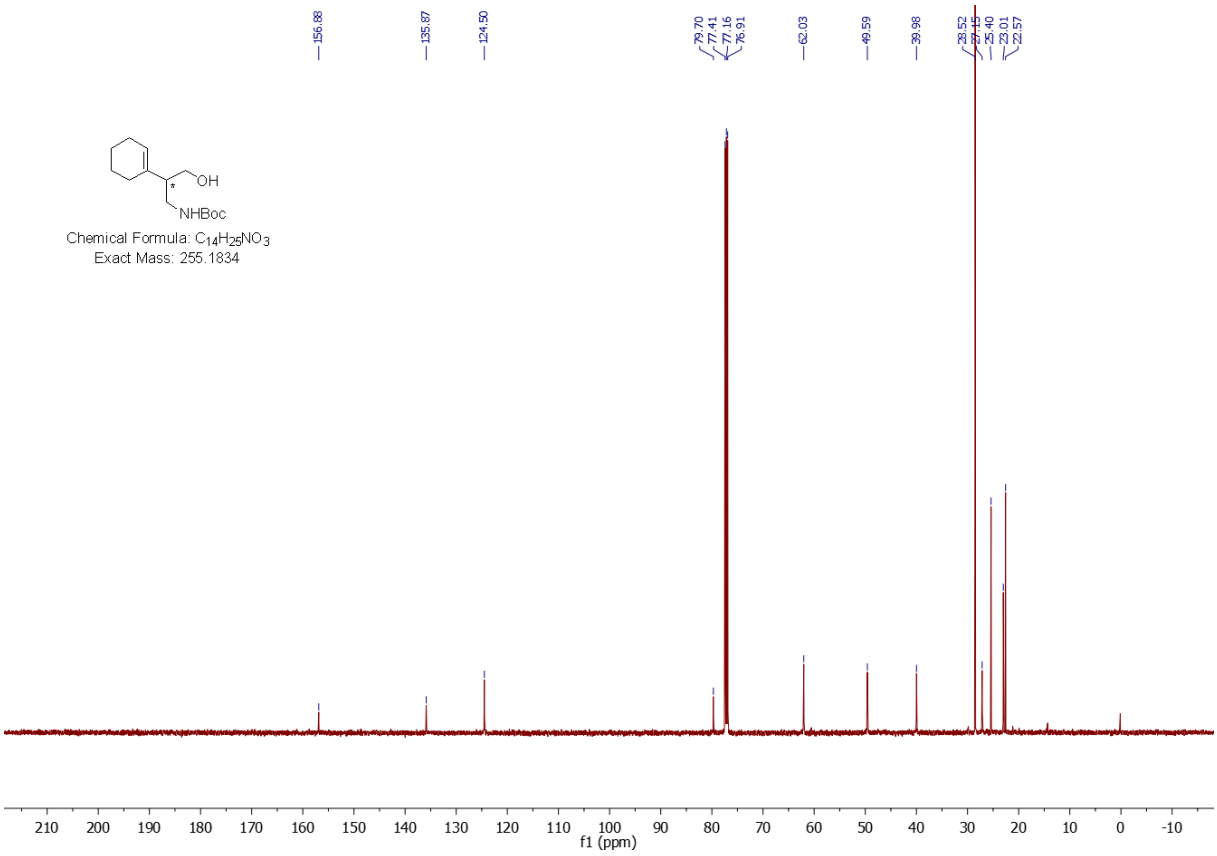

O
N
Boc
Chemical Formula: C19H29NO3
Exact Mass: 319.2147
2.00
2.10
1.07
1.00
2.10
1.18
3.10
1.16
1.18
9.09
3.14
3.08
f1 (ppm)


154.44
144.61
128.11
127.38
126.59
92.26
79.97
77.48
77.16
76.84
56.37
53.90
53.77
30.32
28.87
28.52
28.35
8.85
8.29
O
N
Boc
Chemical Formula: C19H29NO3
Exact Mass: 319.2147
f1 (ppm)


7.26
4.93
4.75
4.71
3.65
3.64
3.62
3.61
3.60
3.58
3.55
3.34
3.33
3.31
3.29
3.28
3.27
3.25
3.23
3.22
2.73
2.34
2.32
2.31
2.29
2.28
1.74
1.44
OH
NHBoc
Chemical Formula: C11H21NO3
Exact Mass: 215.1521
1.00
1.08
0.70
1.97
1.95
0.83
0.96
3.40
9.01
f1 (ppm)


157.02
143.83
113.02
79.85
77.41
77.16
76.91
61.78
49.03
39.76
28.49
21.72
OH
NHBoc
Chemical Formula: C11H21NO3
Exact Mass: 215.1521
f1 (ppm)


7.26
5.48
4.67
3.60
3.59
3.58
3.57
3.57
3.55
3.54
3.53
3.29
3.28
3.27
3.25
3.23
3.22
3.20
3.19
3.18
2.52
2.19
2.18
2.17
2.04
2.02
2.02
1.92
1.63
1.62
1.61
1.60
1.57
1.56
1.55
1.44
OH
NHBoc
Chemical Formula: C14H25NO3
Exact Mass: 255.1834
1.00
0.86
2.06
1.98
0.74
0.92
2.22
2.07
4.36
9.10
f1 (ppm)


156.88
135.87
124.50
79.70
77.41
77.16
76.91
62.03
49.59
39.98
28.52
25.40
23.01
22.57
OH
NHBoc
Chemical Formula: C14H25NO3
Exact Mass: 255.1834
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)